THE USE OF SUGAR DERIVATIVES AS TOOLS OF INDUCTION IN BOTH SOLID AND LIQUID PHASE CHEMISTRY

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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Because they shared my frustration during failure and my joy in times of success, this work is dedicated solely to my parents. For my father, because he is my strength, intelligence, ambition and perseverance. For my father, because he will always be my daddy. To my mother, because she is my heart, compassion, source of humor and dearest of friends. I will always love and admire them both.

ACKNOWLEDGMENTS

God has shaped and molded my life, intricately weaving beautiful, inspirational people into my path for the sake of teaching and learning. These mentors are responsible for many of my personal attributes and dogma. My life has been blessed with many rewards, such as a forgiving environment to make mistakes, the opportunity for a thorough education, the ability to travel to different worlds and exchange dreams with many different people.

Perhaps the most precious gift that God has given me is my family. My grandparents, Eva, Josephine, Salvatore, Merrill and Jonesey, have all known adversity and have all struggled with personal calamities, yet all have persevered in their own way. All of them taught me and nurtured me, as grandparents do, and provided the quiet security that they would always be there to catch me. My grandmother Eva, especially, taught me to listen and to wear the shoes of another. For this lesson in empathy, I am grateful. She is a beautiful, strong woman; she will forever be respected. For my other grandmother, Josephine, although she is gone from my life here on earth, she has forever shaped my love of children and cooking. I will always remember her.

When I close my eyes and think of my daddy, I see the largest of hands and hear the most calming of voices. I think of how those hands cradled me as a child, protected me from all harm and embrace me now as a woman, his daughter. That

voice still fills my ears with sweet dreams of days to come, always coaxing me to go further, push harder and achieve the most unexpected of dreams. This degree was initially just for him, but now I realize it was really another journey I needed to travel to grow in ways I never anticipated. Despite my struggles, no lack of achievement could be conceived as a failure in his eyes. He is truly my number one fan, as I am his.

Although my goals were always driven by my father, I could never have accomplished such a task without my mother. My mother has a wonderful way of bringing me back to the basics, alleviating my stress, and most significantly, making me smile. Despite reminding me to eat well, get lots of sleep, and not to worry, typical attributes of the motherly role, she really is more of a friend than a mother to me. There is no one I enjoy laughing with more than her. The thought of her brings a smile to my face, even in the most challenging of times. I need only to relive the shoe-string/bike incident or the TP she dragged down the aisle during Jurassic Park to remind myself of what is truly important. I look forward to being in close proximity to her again. There are so many lobsters in Maine we need to buy together!

This accomplishment is shared with my sister, Kristen, too. Because of her kindness and selfless nature, she fostered my stubborn, domineering personality, giving me the character traits necessary to persevere in such an environment. If she hadn't conceded in squirrel and glass animals, I probably would have developed some of her compassion! Moreover, the profits collected from my personal yardsales years ago were invested wisely in IPO's and have sufficiently paid for my education.

I am very excited about my new, extended family, Pop, Mom, Amanda, Hiliary and Nick, as well as Nana, Andy and Grandmom. I am happy they can share in the culmination of my graduate education and look forward to letting them know the relaxed, "normal" person that I soon will become.

Two very special friends have shared in two very different times in my life. Natalie Spadorcia is my guardian angel, kindred spirit and sister. I am more than grateful for our friendship. Soon I hope we can do the cafe or Italy, either way the theme is terracotta for life! Time in the lab always went by quicker because of the entertainment and companionship provided by Maria Gallagher. I appreciate the honesty in which we both shared our problems, concerns and dreams. Despite this friendship, Maria has destroyed any of my future endeavors, merely because I do not know how to act "normal" in public anymore. I have lost count of how many times Dr. Deyrup has run into the lab because one of us screamed for no reason. Songs made up on the fly, explosive curses, the ant-ney call, the sam back-up, as well as buki bellies filled an average day in the lab. I have truly enjoyed Maria's friendship and look forward to lunch and baby-shoe shopping weekly in Delaware. She made this time more than bearable. In fact, I dare say it was fun.

Other friends who shared both good and bad will never be forgotten and always will be appreciated for their humor and idiosyncrasies. From a different era, years ago, Katie Murphy and Eugene Morin were true companions during the high school years. During college, very different friends arose, such as the crazy Jeannie Brochi and the thoughtful Dawne Schellar. I give some of my Florida acquaintances the most credit for sticking by me, because these were my most trying times. I will

always cherish the memories I share with Kofi Oppong, Kim Millar, Ben Novak, and Cameron Church. I also enjoyed working on a daily basis with The Lab Ghost, Buck Batson, Ashwin Bharadwaj (the dog), Ravi Ivar (Jimi H.), Ed Whittle, Aarti Joshi, Florent Allais, and past group members Jim Schulte and Kelly Moran. A special thanks to Ravi for his help with many facets of chemistry, particularly the HPLC work.

As for my boss, Eric Enholm, I am forever grateful for his patience with my ever-maturing skills in the lab. Looking back, I have come a long way with regard to chemical knowledge and problem solving. How he ever had the inkling to choose me to develop into a chemist will forever remain a mystery to me. Although my destiny beckons me to the classroom, I will be sure to share with my students the skills he taught me.

Other faculty members were instrumental in my education and development into a professional. Dr. Maria Miliora instilled in me a love of organic chemistry, particularly synthesis, and gave me the confidence to go to graduate school to pursue my dreams of becoming a teacher. Dr. Merle Battiste is a constant source of support and feedback. I marvel at what a thorough teacher he is and aspire to meet such standards in my classroom. I thank Dr. Tomas Hudlicky for his genuine input and care during the pivotal years of my graduate education. Although our teaching methodologies are polarized, I appreciate his efforts and respect his knowledge and style. Dr. Dennis Wright has been a great resource of knowledge. Dennis is a great listener and has helped me with many synthetic challenges. My research, in particular the heteroatom cyclization (Chapter 4), was guided by his influence.

Moreover, I appreciate the use of both THUD's chiral column and Dennis' HPLC for the heteroatom cyclizations. Last, my committee members Dr. David Powell and Dr. Kenneth Sloan were instructional at the peaks of my graduate career.

Last, this work would have been accomplished more easily if I hadn't met my husband, Andrew, until after my graduate career. In all honesty, Andrew, has been the most pleasant of distractions. Our similar love of family, career, athleticism, and travel promise a long and happy future together. Soon, after running this gauntlet, we can concentrate on being husband and wife, parents and an inseparable couple. Andrew is the reward for all of my hard work. He is the soulmate that I have waited for, my best friend, and loving partner in crime. He is my future. Baby, I will love you always.

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By

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Chairman: J. Eric Enholm
Major Department: Chemistry

The use of chiral auxiliaries for asymmetric transformations is a growing research area; however, the application of carbohydrates as chiral templates for free radical reactions has not been studied sufficiently. For the first time, these investigations illustrate the utility of two carbohydrate derivatives as sources of asymmetry for 5-exo hexenyl and 6-exo heptenyl free radical cyclizations.

The employment of a carbohydrate scaffold for a stereoselective, 5-exo hexenyl radical cyclization was explored. A survey of optimal solvents, radical initiators, temperatures, Lewis acids, and auxiliaries ensued. Diastereomeric ratios as

high as 100:1 were achieved with an appended (+)-isosorbide moiety and 70:1 for the (+)-xylose chiral template. The newly generated chiral center of both carbohydrate-mediated cyclizations are of the (S)-configuration.

After the success of the above experiments, the carbohydrate template-mediated free radical cyclizations were translated to a polymer-supported manifold. A norborene cycloimide was constructed that had (+)-isosorbide tethered to the polymerization precursor. A ring opening metathesis was performed, yielding a polymer with a carbohydrate scaffold on each monomer unit. Radical cyclization, both a 5-exo hexenyl and 6-exo heptenyl, were explored within this polymer medium. For the formation of six-membered rings, Lewis acids such as magnesium bromide etherate and zinc chloride were successful in enhancing the selectivity to 86% and >99% enantiomeric excess, respectively.

A heteroatom derivative to the liquid phase carbo-5-exo hexenyl radical closures was constructed and cyclized. The selectivity observed in the radical cyclization was surprisingly high, yielding enantiomeric ratios as high as >99% for the zinc chloride mediated closure.

Last, a tartrate derivative was appended to a non-crosslinked polystyrene support in hope of performing the first asymmetric Grignard reaction on this non-crosslinked polystyrene support (NCPS) technology. Cleavage of the final α-hydroxy ketal was fraught with difficulty. However, the ability to translate acetal chemistry to a non-crosslinked soluble polymer environment was established.

CHAPTER 1
INTRODUCTION

History of Free Radicals

A generally accepted theory is that Gomberg[1] identified the first radical in 1900 in the form of a trivalent carbon compound, triphenylmethyl. However, the beginnings of synthetic transformations by radical pathways did not appear until 1937 with the work of Hey and Waters[2] in the area of homolytic phenylation of aromatic substrates, as well as with Kharasch[3] and the regioselectivity of HBr addition to alkenes. An interesting note in cyclization reactions is that many aspects of radical chemistry were outlined in detail by Surzur[4] and co-workers and Julia[5] in the 1960s, but were not applied to synthetic endeavors until the 1980s by Stork, Curran and others.[6]

A highly reactive radical species is generated when a covalent bond is cleaved homolytically. This radical intermediate is neutral in nature, therefore solvation effects, racemization at adjacent centers and unwanted synthetic transformations of labile functional groups are less pertinent issues with this type of chemistry. Although radicals are considered neutral species, their reactivity is vast, thus making carbon-carbon bonds via free radicals a powerful tool in a synthetic chemist's repertoire.

Free Radical Cyclizations

Radical cyclizations usually consist of intramolecular additions to double or triple bonds. Intramolecular radical closures have been widely used in organic synthesis only since the beginning of the 1980s.[6] Many mechanistic studies have shown that a wide range of mono- and polycyclic products can be obtained with regio- and stereoselectivity: natural products, alkaloids, antibiotics, etc.[6] This free

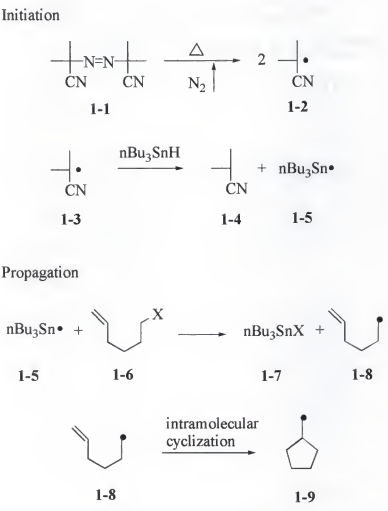


Figure 1-1. Tributyltin hydride radical cyclization mechanism.

radical transformation can be applied to many precursors, because the conditions are neutral and therefore compatible with most functional and protecting groups. For instance, very often a hydroxy functionality does not need to be protected before a radical transformation. Tin hydride is an extremely mild and selective radical propagator and perhaps the most common reagent for free radical reactions.[7,8] The mechanism of radical cyclization involves a controlled chain reaction (Figure 1-1). The preliminary step of the mechanism involves initiation of the free radical process, usually by homolytic cleavage of labile bonds with heat or light. Some common radical initiators include azobisisobutyronitrile (AIBN), triethyl borane/oxygen (for lower temperature studies), and a wide variety of peroxides. A site-specific radical is generated from an organic substrate by atom or group abstraction. The radical then reacts with tin hydride to generate the reduced product or with itself to obtain a cyclized adduct. The transferability of various substrates X in Figure 1-1 to the tin

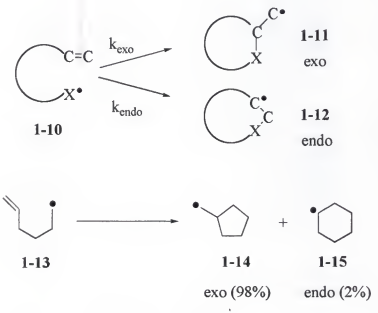


Figure 1-2. Exo vs. endo radical cyclizations.

radical is generally in the order of I > Br > SePh = OC(S)SMe > Cl > SPh.[8,9,10] Although steric interactions influence the cyclization energy barrier, highly complex molecules nonetheless can be constructed through radical additions.

When radical closures occur on a double bond, the radical center is either external to the newly formed bond (exo) or resides internally in the generated cyclic structure (endo). Of the two possible cyclizations, exo **1-11** and endo **1-12**; generally the former is preferred kinetically (Figure 1-2).[11] Cyclization reactions are sensitive to the same thermochemical, steric and polar effects as intermolecular additions, but they are subject to an additional constraint of ring formation.

Free radical processes generally are preferred by some chemists because of the pH neutrality of the reaction conditions. For instance, much work has been done by Enholm and co-workers on the formation of tin enolates by radical methods.[12] This mild procedure is preferential because the formation of a metal enolate via a strong base most likely would be intolerant of other functionalities in the molecule. However, this distinction is not the only benefit that entices chemists to free radical procedures. For example, despite an unfavorable entropy factor, one can obtain macrocyclization (>10-membered ring) through free radical processes.[13] Moreover, substituents on the cyclization precursor have a different effect on the rate of closure, the regioselectivity (exo vs. endo), and the stereoselectivity, allowing investigators many options for constructing complex molecules.[13] Last, if the initial radical is stabilized, the cyclization becomes reversible and the products are governed by thermodynamics with a preference for the 6-membered ring.[13] This gives the researcher additional control of the reaction conditions. However, in most cases, the

5-exo-hexenyl product predominates whenever possible. These interesting features of free radical chemistry intrigue researchers in the field.

5-Hexenyl Radical Cyclizations

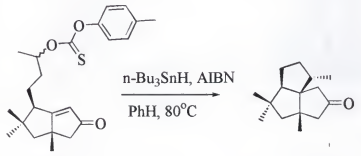
The hexenyl radical is unique in that radical cyclization predominates and favors exo regioselectively. According to Baldwin, exo-cyclizations, which account for a 5-membered ring closure, are favored over endo-cyclizations, that result in cyclohexyl systems.[11] Less favorable entropies and steric effects in the 6-endo cyclizations transition state such as 1,3 diaxial interactions also account for the favored formation of the 5-exo cyclization adduct.[14,15] Because of these energy factors and steric considerations, cyclizations usually are faster for the formation of 5-membered rings than for any other ring size. Since the 5-exo-hexenyl radical cyclizations are twenty times faster than 6-exo-heptenyl closures, 5-membered ring formation is less prone to competitive side reactions than the slower reacting 6-membered radical closures.[13] An additional advantage to the formation of cyclopentyl systems is the predictable and outstanding regioselectivity that is observed. Moreover, the stereoselectivity of the reaction can be foreseen successfully by the Beckwith transition state model.[16]

According to this theory, the early transition state of a 5-exo radical cyclization resembles a cyclohexane ring, preferring a chair to boat conformation and pseudo-equatorial substituents to pseudo-axial substituents (Figure 1-3).

Furthermore, the Beckwith model suggests that C1 or C3 substitution of the 5-hexenyl radical gives primarily cis-disubstituted cyclopentanes, whereas C2 or C4 substitution results in a trans molecule.[17] This stereoselectivity is explained by a transition state in the chair configuration, the substituents preferably being in the equatorial position.

Figure 1-3. Beckwith's chair model for the transition state of a 5-exo-hexenyl radical closure.

Through the formation of these cyclopentyl skeletons, highly complex or hindered formations can result. For instance, in Nagarajan's synthesis of an angular



1-16 **1-17**

Figure 1-4. Nagarajan's synthesis of an angular triquinane silphinene.

triquinane silphinene, a neopentyl/quartinary center is produced (Figure 1-4).[6,7] In this case, a derivative of *p*-tolylthionocarbonate **1-16** was treated with tributyltin hydride. The generated radical added stereoselectively to the double bond of the enone, yielding angular triquinane **1-17**, exclusively. This radical, intramolecular cyclization was among the first approaches toward the tricyclo[6.3.0.$0^{1,5}$]undecane skeleton and is a clear example of the complexity that can be achieved with the versatile radical cyclization methodology.

6-Heptenyl Radical Cyclizations

Although the formation of five-membered rings is favored in the radical closure process, six-membered rings are accessible in high yields in a 6-heptenyl cyclization. In fact, the first example of a radical closure with tin hydride was a 6-heptenyl cyclization as opposed to the more utilized 5-membered ring closure.[4] Because 6-membered ring formation reactions are slower, they are subject to competitive formation of reduced, uncyclized byproducts. Many 6-heptenyl radicals are also subject to intramolecular 1,5-H atom transfer. Simple 6-exo radical cyclizations are also less regioselective. For the 5-hexenyl radical, 5-exo cyclizations are fifty times faster than 6-endo cyclizations, however for the 7-heptenyl radical, 6-exo cyclizations are only six times faster than 7-endo cyclizations. The slower reaction rates often cause diminished reactivity concomitant with decreased

chemoselectivity. However, the formation of six-membered rings under neutral pH, mild conditions is a much-sought methodology by synthetic chemists.

Chiral Auxiliaries and Free Radical Chemistry

The application of chiral scaffolds in free radical chemistry is a relatively new area of investigation. Although chiral auxiliaries have received great attention and success in an anionic manifold, it was the extrapolation of chiral scaffolds to free radical processes that expanded stereoselectivity to this realm of study.[18] A wide variety of chiral moieties have been explored in the literature as of late (Figure 1-5).[19]

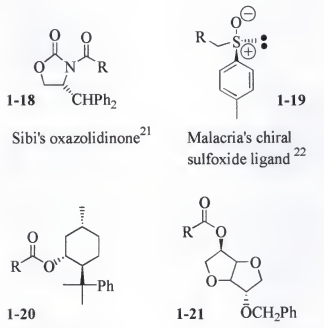


Figure 1-5. Common functionalities for free radical chiral auxiliaries.

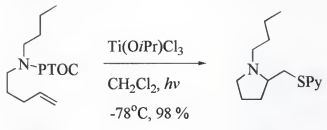
Curran's derivative of Kemp's triacid has received great acclaim for its selectivity, although the construction of the appending molecule is quite tedious.[20] Many investigators have employed Evan's oxazolidinone; perhaps most notable was Sibi's attempts at intermolecular, stereoselective, β-radical additions with such a template.[21] Other scaffolds such as sulfoxides and chiral esters also were utilized in radical transformations with moderate success.[22,23] Carbohydrate derivatives, despite their complex chiral nature and ready availability, curiously are under-exploited in this realm of chemistry. This dissertation contains the first studies in this area. Sugar derivatives have been regarded as too complex to be useful in asymmetric synthesis, constructed of too many chiral centers, and with too many functional groups. It was thought that the chiral information they contain could not be exploited in a stereo-differentiating selection process in an organized and surveyable fashion. Therefore, carbohydrates have been transformed and converted into diverse, interesting chiral natural products, as opposed to taking advantage of their inherent asymmetry for auxiliary purposes.[25,26] The steric, stereoelectronic and coordinating properties of carbohydrate templates also can be used selectively to attain high levels of induction in processes such as Diels Alder reactions, [2+2] cycloadditions, cyclopropanations, and Michael additions, however, their application to free radical chemistry remains mostly unexplored.[27]

Although the asymmetric influence of the appended chiral auxiliary is apparent in the free radical process, asymmetric induction has not been all that successful in this area of chemistry. In fact, it was Renaud and Porter that

demonstrated the powerful tandem of chiral auxiliaries and Lewis acids in free radical reactions.[18,28]

Lewis Acid and Stereoselective Radical Transformations

Before the utility of the combination of Lewis acids and chiral auxiliaries had been realized, the first application of Lewis acids in radical reactions involved polymerization reactions.[29] It was observed in these studies that the Lewis acid could control the reactivity of radicals. This effect has not been applied to synthetic radical chemistry until fairly recently. An early example concerns the cyclization of aminyl radical precursor **1-22**, where PTOC is pyridine-2-thion-N-oxycarbonyl (Figure 1-6).[30] Under strictly neutral conditions (no Lewis Acid), the cyclic product **1-23** is not



1-22 **1-23**

Figure 1-6. Lewis acid activation of an aminyl radical cyclization.

observed. However, by employing the titanium metal complex the cyclization product **1-23** is obtained in quantitative yield. The amount of product formed exceeds the amount of Lewis acid used, implicating a potential, catalytic cycle.[31]

The role of Lewis acids in radical reactions is thought to be multi-functional. Commonly, Lewis acids are responsible for substrate activation, as in the above case, for radical addition, resulting in higher yields of product.[18] Moreover, Lewis acids are responsible for incorporating stereoselectivity as the mechanistic details of radical transformations are being elucidated.[18] Either chiral, designer Lewis acids are employed or they are used in combination with chiral auxiliaries to achieve such selectivity. For instance, in the case of the popular oxazolidinone scaffold, a bidentate Lewis acid is suggested to control the rotamer population so that the N-enolyloxazolidinone can attain a conformation that favors cyclization of **1-24** (Figure 1-7).[21] It was this powerful combination that instigated the use of amide, ester, and sulfoxide moieties as potential chiral auxiliaries. Chelation by a Lewis acid, not only

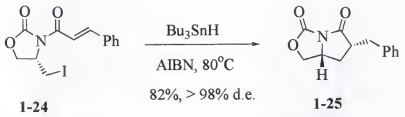


Figure 1-7. 5-exo-hexenyl radical cyclization where Bu_3SnI is the *in situ* Lewis acid.

provides a steric bias towards the incoming radicophile, but also locks the chiral scaffold into a preferred conformation or rotameric form.[21] It is this combination that has coaxed many synthetic chemists back to the benefits of free radical chemistry, gaining both neutrality in reaction conditions and stereoselectivity in a free radical transformation. Moreover, it was this combination that elucidated the powerful potential of carbohydrate derivatives as chiral scaffolds. The complexation of Lewis

acids, which result in an organized arrangement of the functional groups of a carbohydrate, seemed paramount to effective use of sugar templates as stereo-differentiating tools in asymmetric synthesis.[19]

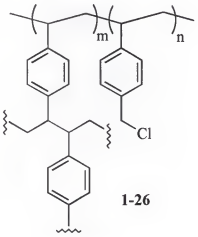
Soluble-Support and Asymmetric Transformations

The growth of polymer-supported chemistry is directly correlated with industrial need for diverse libraries of enantiomerically pure compounds for many areas, including lead identification in the drug delivery process. A multitude of options for polymer-supported chemistry are revealed from this expanding field. For instance, investigators must choose soluble or insoluble polymer matrices; whether to link their substrate, reagent, or catalyst directly to the polymer backbone; and last, explore considerations of substrate cleavage, recovery, linker selection, reagent stoichiometry, and reaction analysis. Inherent in these decisions is the wide variety of advantages associated with polymer-supported reactions, including, but not limited to, increased ease of product isolation and purification. A rarely studied facet of polymer-supported chemistry is the ability to create a stereo-differentiating reaction environment within the polymer backbone. This can be achieved by directly linking chiral scaffolds or catalysts to the polymer chain.[32,33,34,35]

The initial choice between soluble and insoluble support can be alleviated by considering the chemical environment necessary for the reaction. The ultimate difference in the solubility of the two polymers results from linking the polymer

backbone into a rigid framework, affording a cross-linked polymer. This rigidity prevents solvation of the polymer, allowing the solid phase resin to provide an insoluble solid surface for reactions to occur. Non-cross-linked polystyrene has a single, linear backbone, where the repeat monomer is not connected to other segments of the polymer framework. This type of polymer chain increases solvation and thus, traditional liquid phase chemistry is possible (Figure 1-8).

A non-crosslinked polystyrene polymer support was developed by Merrifield in the 1970s for peptide synthesis, however, its application to standard organic



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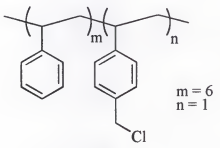


1-27

Cross-linked Polymer
Solid Phase Organic Chemistry (SPOC)

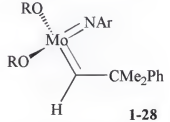
Non-Cross-linked Polymer
Liquid Phase Organic Chemistry (LPOC)

Figure 1-8. An illustration of the rigid cross-linked polymer vs. the flexibile non-cross-linked polymer.

synthesis has been not studied sufficiently.[36] Researchers have found that the rate of coupling reactions for the soluble non-crosslinked polymer is similar to classical liquid phase peptide synthesis, translating to a reaction rate two orders of magnitude greater than common insoluble solid phase reactions.[36] Other merits of the non-

crosslinked polystyrene support (NCPS) polymer include (1) inexpensive preparation; (2) solubility in common organic solvents (i.e., ethyl acetate, benzene, chloroform, methylene chloride, tetrahydrofuran), additionally, NCPS is insoluble in methanol and water, thereby, facilitating purification of reaction intermediates; (3) polymer bound substrates can be analyzed by ^{1}H NMR spectroscopy without cleavage from the polymer support; and (4) the amount of polymer loading can be controlled.[36]

Similar to the precipitation of NCPS, ring opening metathesis polymerization (ROMP) produces a soluble polymer that precipitates in methanol. Taking advantage of the inherent strain of the norborene system, Grubbs and Schrock both devised metal alkylidene catalysts that are driven by the entropic factors of ring opening and the release of a small molecule, commonly ethylene (Figure 1-9).[37] The catalyst



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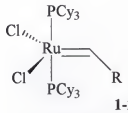
Ar = 2,6 diisopropyphenyl
RO = $(CF_3)_2(CH_3)CO$



1-29

R = CH=CPh_2
R = Ph

Figure 1-9. Olefin metathesis catalysts by Schrock and Grubbs respectively.

developed by Grubbs and co-workers is highly reactive, readily tolerates polar functionality and can effect a living polymerization.[38] Laura Kiessling elaborated on such a catalyst by polymerizing a highly oxygenated, sugar derivatized, norborene imide.[39] Because of the tolerant nature of the catalyst, carbohydrate-polymer

precursors can be utilized, foreshadowing the potential of sugar auxiliaries on a soluble polymer backbone. Although Kiessling and others have been successful synthesizing and polymerizing such systems, the ROMP process takes many hours to several days to complete, resulting in moderate to high molecular weight polymers, depending on the monomer precursor.

Another advantage to ROMP polymers is their loading capacity. Compound loading on insoluble and some soluble resins can be low; therefore quite a large amount of polymer is required to obtain only a few milligrams of product after

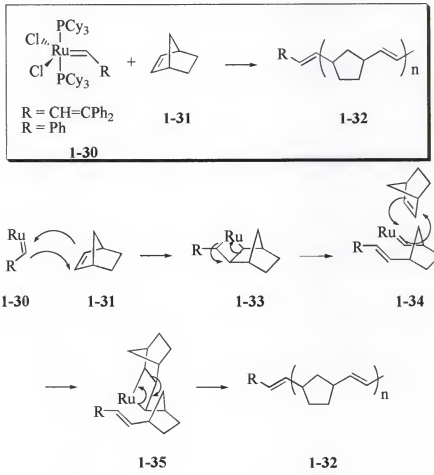


Figure 1-10. ROMP mechanism involving the ruthenium metallocene.

cleavage. With ROMP, a stoichiometric amount of loading sites can be incorporated into the polymer backbone, therefore the polymer consists solely of repeating monomer units, making loading quantitative.[40]

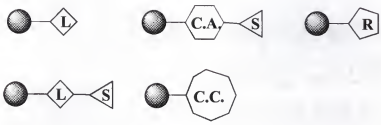
Living, ring-opening metathesis polymerization leads to polymers of the general structure $R^1M_nR^2$, with M being the repeating unit and n the degree of polymerization. The end groups R^1 and R^2 result from the initiation step, which is the insertion of the first monomer in the ruthenium alkylidene complex and the quenching of the catalytic cycle with the capping additive. The mechanism of the ring-opening polymerization is illustrated in Figure 1-10.

The only noted advantage of insoluble support systems as opposed to soluble matrices, despite the disadvantages previously stated, is that of recovery. Because precipitation of a soluble polymer relies on several factors such as solvent choice and the concentration of the filtrate, a guarantee of complete recovery of the insoluble beads is quite attractive. However, all other beneficial attributes reside with soluble polymer-supports.

The next tier of sophistication when considering polymer-supported chemistry is the logistics of the reaction. Figure 1-11 illustrates the many combinations of reaction components that can be explored and manipulated by the investigator, fully exploiting the inherent substrate functionalities and reaction characteristics. There are many excellent reviews on substrate linkers, supported reagents and chemical transformations on polymer-support.[41]

Conclusions

The following work combines the above-mentioned methodologies of free radical cyclization, asymmetric induction via a chiral auxiliary, stereoselectivity enhancement by chelated Lewis acids and the benefit of soluble-polymer supports. A survey of these pertinent organic topics has resulted in optimized conditions of yield augmentation, high stereoselectivity and efficient purification of tributyltin hydride-mediated free radical cyclizations.



where:

represents the polymer support — R represents a reagent

L represents the chemical linker — S represents the substrate

C.A. represents a chiral auxiliary — C.C. represents a chiral cataylst

Figure 1-11. A pictorial representation of some of the various chemical possibilities when considering a solid phase reaction manifold.

Chapter 2 of this work presents our initial studies of a 5-exo hexenyl radical cyclization in the presence of two different carbohydrate derivatives and various Lewis acids. The goal of this study was to optimize a protocol for this radical

cyclization reaction so that the extrapolation of our results to the soluble polymer methodology would be fruitful. Reaction parameters such as solvent, radical initiator, Lewis acid, chiral auxiliary and temperature were explored thoroughly. The optimized procedure is discussed herein.

Chapter 3 examines the adaptation of the liquid-phase 5-hexenyl radical cyclization reaction to a soluble polymer support. The polymer was constructed via ring opening metathesis, starting from a carbohydrate functionalized norborene cycloimide. Moreover, the success of a 6-heptenyl radical closure on this support also is reported. The advantages of mounting these tributyltin hydride-mediated cyclizations onto polymer support, such as ease in purification and removal of residual tin by-products, are discussed.

Chapter 4 illustrates the unprecedented success of (+)-isosorbide as a chiral auxiliary in a heteroatom 5-hexenyl cyclization. In this study, the cyclization methodology precursor was changed, replacing the possibe template benzene ring with a sole oxygen atom. It was our hope that the lone pair of the oxygen also would participate in the Lewis acid, (+)-isosorbide chelate, providing a high level of stereoselectivity in the radical closure. Enantiomeric excesses, based on HPLC studies using a chiral L-leucine chiral column, as high as 99% were observed.

Lastly, Chapter 5 presents earlier studies regarding polymer-supported ketal chemistry. It was our hope to document the first example, at that time, of a stereoselective Grignard reaction on polymer support. The asymmetry was a result of a homochiral tartrate diol appended to a non-crosslinked polystyrene support. Although the utility of acetal chemistry was demonstrated on this soluble polymer,

the stereoselective nature of the Grignard reaction was ambiguous because of an inability to cleave the chiral adduct from the polymer support. Postulations are discussed.

CHAPTER 2
LEWIS ACID PROMOTED 5-HEXENYL RADICAL CYCLIZATIONS IN THE PRESENCE OF SUGAR CHIRAL AUXILIARIES

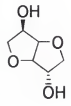
Introduction

Nucleophilic conjugate addition reactions offer synthetic chemists a well-documented and reliable means of carbon-carbon bond formation.[42] Positive synthetic benefits, such as neutral reaction conditions and tolerance of various functional groups, can be obtained when carbon-centered radicals react with α,β-unsaturated carbonyls.[21] Intermolecular free radical reactions have found popularity because of their ability to afford reliable stereoselectivity. The observed selectivity is attributed to the use of either chiral Lewis acids[43] or appended chiral auxiliaries.[44] The success of the latter has broadened radical studies to encompass the survey of potential chiral auxiliaries, effect of temperature and solvent, and addition of Lewis acids.[21,44]

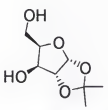
Although intermolecular β-radical additions have been studied extensively,[21,45,46,47,48] diastereoselective free radical cyclizations are investigated far less in the literature.[49,23] Badone and coworkers demonstrated the potential of such a transformation by tethering a chiral oxazolidinone to both a bromo and xanthate unsaturated carbonyl substrate. Diastereomeric ratios as high as 82:18 were

observed.[50] Another report issued by Nishida illustrated the effectiveness of an intramolecular addition of alkenyl radicals to the β-position of 8-phenylmethyl, α,β-unsaturated esters. Diastereomeric ratios as high as 98:2 and an isolated yield of 42% were achieved in the presence of Lewis acids.[23] With ratios up to 100:1, the 5-hexenyl radical cyclization following in this text stands out as one of the most highly diastereoselective radical cyclizations resulting from an appended chiral template. Moreover, the use of a sugar chiral auxiliary is unprecedented in such a transformation.

A common auxiliary used extensively in many anionic and some radical reactions is the expensive chiral oxazolidinone moiety.[51,52] To circumvent the issue of cost, our investigations examined the inexpensive and commercially available sugars (+)-isosorbide and (-)-xylose monoacetonide. As illustrated in Figure 2-1, both



2-1 (+)-isosorbide



2-2 (-)-xylose derivative

Figure2-1. Isosorbide and monoacetonide xylose as potential chiral auxiliaries.

carbohydrate compounds offer highly oxygenated structures, providing multiple sites for metal (M) chelation. Asymmetric Diels-Alder reactions have successfully utilized (+)-isosorbide and (-)-xylose, we reasoned therefore, that these sugars should function well as chiral templates in a 5-hexenyl radical cyclization.[53, 54, 55]

To date there has been little utilization of the inherent chiralty of carbohydrate derivatives as chiral auxiliaries. In fact, sugars are commonly percieved as starting substrates from the chiral pool to be manipulated and functionalized rather than providing asymmetric induction.[56] Much effort has been put forth in the area of transforming carbohydrates to useful synthetic precursors.[56] It is the multi-oxygenated nature of sugars that prescribes their use as potential chiral auxiliaries,

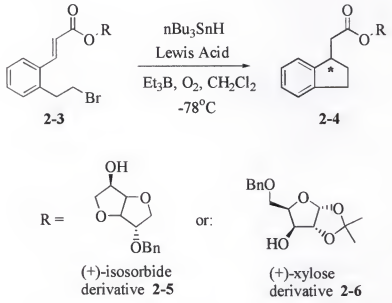


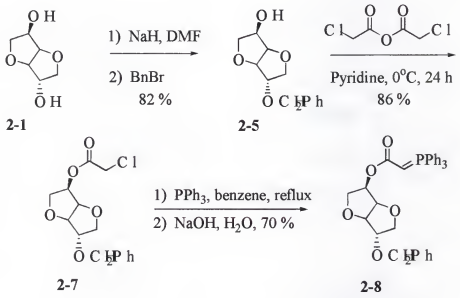
Figure 2-2. 5-Hexenyl radical cyclization of carbohydrate appended unsaturated ester precursors.

especially as our understanding of Lewis acid coordination and asymmetric induction expands. The purpose of this investigation, shown in Figure 2-2, involved a study of these carbohydrate derivatives as chiral scaffolds in free radical cyclizations, particularly at low temperatures (-78 °C). The methodology investigation utilized an α,β-unsaturated chiral ester as the cyclization precursor, tributyltin hydride (TBTH)

as the radical propagator and triethylborane and oxygen as the radical intiator. Many reaction conditions were explored, including a variation on radical initiators, solvents, Lewis acids, and temperatures. The optimized protocol for 5-exo-hexenyl radical cyclizations in the presence of such carbohydrate auxiliaries is discussed herein.

Synthesis of Methodology Precursors

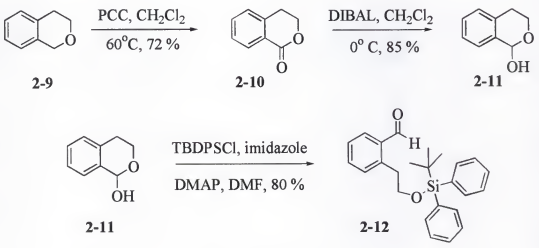
The methodology precursor is an α,β-unsaturated chiral ester; therefore, a Wittig reaction constructed the main framework of the molecule. A carbohydrate-



Scheme 2-1

derived Wittig reagent was synthesized in three steps from commerically available (+)-isosorbide as illustrated in Scheme 2-1. Monobenzylation of (+)-isosorbide **2-1**

was achieved by deprotonation using sodium hydride, followed by trapping of the alkoxide anion with benzyl bromide in 82% yield.[53] The remaining hydroxyl functionality was converted to chloroester **2-7** using chloroacetic anhydride in pyridine and chloroform. Transformation to the corresponding ylide **2-8** was achieved by heating **2-7** in the presence of triphenylphosphine followed by deprotonation by sodium hydoxide. Purification of **2-8** was achieved through a series of extractions.

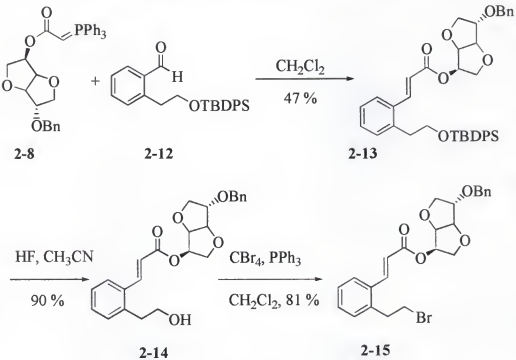


2-9 **2-10** **2-11** **2-11** **2-12**

Scheme 2-2

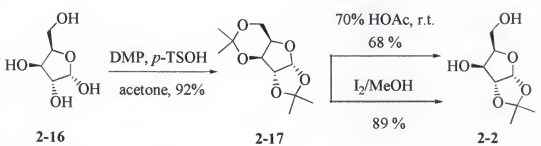
Aldehyde **2-12** which was synthesized from commerically available isochroman (Scheme 2-2) was then coupled with Wittig reagent **2-8**. Isochroman **2-9** was first oxidized by pyridiniumchlorochromate (PCC) followed by reduction with diisobutylaluminiumhydride (DIBAL) to lactol **2-11** in 61% yield.[55] The aromatic lactol was then trapped as an aldehyde with a bulky silylating agent, *tert*- butylchloro diphenylsilane, imidazole and dimethylamino pyridine in DMF. The desired aldehyde was achieved in three steps with an overall yield of 50%. The unsaturated

chiral ester **2-13** resulted when Wittig reagent **2-8** and aldehyde **2-12** were combined in a 1M solution in methylene chloride. Further manipulations included deprotection of the silyl ether with HF in acetonitrile. Conversion of the corresponding alcohol **2-14** to the methodology bromide precursor **2-15** was achieved in 89% yield with



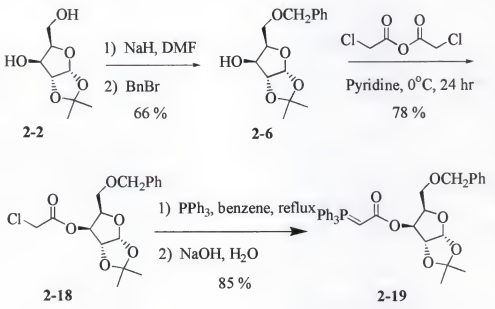
Scheme 2-3

carbon tetrabromide, triphenylphosphine in methylene chloride (Scheme 2-3). The unsaturated (-)-xylose ester monoacetonide was achieved in an analogous



Scheme 2-4

fashion. Commerically available (-)-xylose acetonide **2-2** was monobenzylated and esterified, similiar to the isosorbide moeity. Although the monoacetonide is commercially available, (-) xylose **2-16** is a significantly less expensive alternative. (-) Xylose can be protected as the diacetonide using *p*-toluenesulfonic acid and dimethoxypropane in acetone. The six-membered acetonide can be selectively cleaved with either a 70% concentration of acetic acid or iodide in



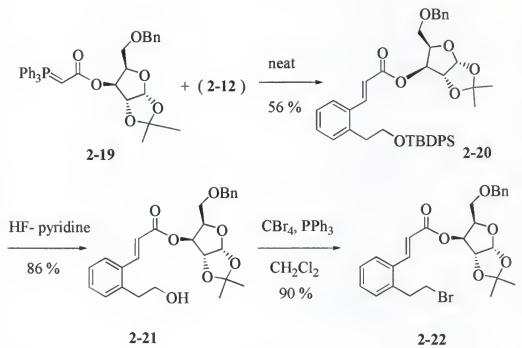
Scheme 2-5

methanol to produce the desired monoacetonide **2-2** (Scheme 2-4). Monobenzylation and esterfication of the xylose moiety allowed Wittig reagent **2-19** to be synthesized after reflux in benzene with triphenylphosphine followed by a basic workup (Scheme 2-5). The Wittig reaction proceeded in a higher yield than the isosorbide counterpart, providing the unsaturated (-)-xylose ester **2-20** in 56%. The TBDPS silyl protecting group was removed by a buffered solution of HF in pyridine. This reagent differed from the isosorbide synthetic scheme due to the acid labile acetonide on the xylose

substrate. The alcohol **2-21** was transformed to the bromide methodology precursor **2-22** in 90% yield Scheme 2-6.

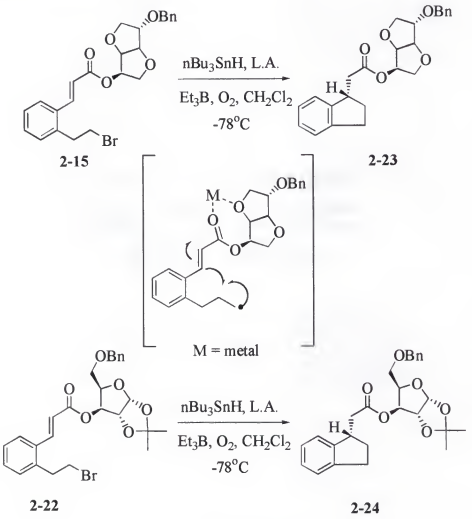
Results and Discussion

Once the unsaturated bromoester of each carbohydrate derivative had been synthesized, various reaction conditions for the 5-hexenyl radical cyclization were explored. It was determined that temperature, radical initiator, solvent, and Lewis acids would be the variables of this study. The distereometric ratios of the cyclized adduct were obtained *via* GC and HPLC.



Scheme 2-6

As demonstrated in Scheme 2-7, the cyclization was initiated by the formation of the tributyltin radical followed by abstraction of the bromide atom on the precursor molecule, thus triggering an intramolecular cyclization at the β- position of the α,β-unsaturated chiral ester. The selectivity of this cyclization is dependent on many factors; particularly Lewis acid (L.A.) selection and reaction temperature, as illustrated in Table 2-1. Because of the temperature dependance of AIBN, triethylborane and oxygen were utilized for the lower temperature studies. As expected, the radical cyclization of the (+)-isosorbide moeity proved to be more selective for a particular



Scheme 2-7

diastereomer at lower temperatures. The diastereomeric excess(d.e) ranged from 1.6:1; a nearly unselective process at 80 °C, to a more discriminating 3:1 at -78 °C. When a Lewis acid was employed, distereomeric ratios increased substantially, peaking at >100:1. These results suggest the possible formation of a potentially activated metal chelate with the appended isosorbide auxiliary. It is postulated that a seven membered chelate exists between metal and sugar, however, crystalographic or NMR data would be needed to confirm this claim. Of the Lewis acids studied, zinc chloride and

Table 2-1. Diastereomeric ratios of the (+)-isosorbide mediated 5-hexenyl radical cyclization.

	Radical Initiator	*T*, °C	Solvent System	Lewis Acid	d.e.
1	AIBN	80	Benzene	N/A	1.6 : 1.0
2	Et_3B, O_2	25	CH_2Cl_2	N/A	1.75 : 1.0
3	Et_3B, O_2	0	CH_2Cl_2	N/A	2.2 : 1.0
4	Et_3B, O_2	-78	CH_2Cl_2	N/A	2.9 : 1.0
5	Et_3B, O_2	-78	CH_2Cl_2 / ether	$MgBr_2$ OEt_2	100 : 1.0
6	Et_3B, O_2	-78	CH_2Cl_2 / THF	$ZnCl_2$	100 : 1.0
7	Et_3B, O_2	-78	CH_2Cl_2	$Yb(OTf)_3$	1.6 : 1.0
8	Et_3B, O_2	-78	CH_2Cl_2	Et_2AlCl	7 : 1

magnesium bromide etherate proved to be the most effective with diastereomeric values as high as 100:1. Also interesting was the relatively poor influence the lanthanide Lewis acids had on the selectivity of the cyclization. Recently, many literature accounts have exemplified the great activation and chelating ability lanthanides possses in free radical chemistry.[21,28] It is noted that reaction completion was more readily observed by TLC in the ytterbium and europium examples

compared with the other Lewis acids studied. Perhaps the accelerated rate of reaction noticed with the lanthanides can account for the poor selectivity observed in these examples.

The (-)-xylose monoacetonide sugar proved successful as well (Table 2-2). Again, a temperature dependance was illustrated for these cyclizations. In some cases, a cosolvent, either ether or tetrahydrofuran, was necessary to solubilize the Lewis acid. Lewis acids, such as diethylaluminium chloride and titanium

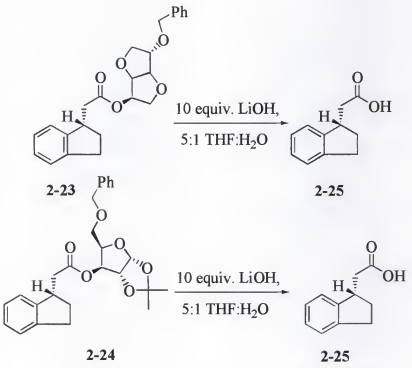
Table 2-2. Diastereomeric ratios of the (-)-xylose monoacetonide mediated 5-hexenyl radical cyclization.

	Radical Initiator	***T*, °C**	**Solvent System**	**Lewis Acid**	**d.e.**
1	Et_3B, O_2	25 °C	CH_2Cl_2	N/A	9:1
2	Et_3B, O_2	0 °C	CH_2Cl_2	N/A	5:1
3	Et_3B, O_2	-78 °C	CH_2Cl_2	N/A	7:1
4	Et_3B, O_2	-78 °C	CH_2Cl_2 / ether	$Eu(OTf)_3$	2:1
5	Et_3B, O_2	-78 °C	CH_2Cl_2 / THF	$ZnCl_2$	6:1
6	Et_3B, O_2	-78 °C	CH_2Cl_2	$AlEt_2Cl$	60:1
7	Et_3B, O_2	-78 °C	CH_2Cl_2	$TiCl_4$	70:1
8	Et_3B, O_2	-78 °C	CH_2Cl_2	$Yb(OTf)_3$	12:1
9	Et_3B, O_3	-78 °C	CH_2Cl_3	$SnCl_4$	decomposed

tetrachloride, provided d.e. ratios as high as 60:1 and 70:1, respectively. Surprisingly, zinc chloride, an effective chelating metal for the isosorbide sugar, played a minor role in controlling the stereochemistry of the carbohydrate- mediated cyclization. For both sugars, the lanthanides tried, such as europium(III) trifluoromethane sulfonate

and ytterbium(III) trifluoromethane sulfonate, were ineffective in enhancing the selectivity of the cyclization. Although the reaction details vary slightly, both carbohydrate derivatives, (+)-isosorbide and (-)-xylose, demonstrate their utiliy as chiral templates for intramolecular free radical cyclizations.

After the diastereomeric ratios of each reaction parameter set had been determined, elucidation of the newly formed chiral center was investigated. The



Scheme 2-8

known literature optical rotation of indanoic acid allowed such an opportunity.[48] Cyclized isosorbide adduct **2-23** and xylose adduct **2-24** were subjected to saponification conditions using lithium hydroxide in water/THF (Scheme 2-8). Carboxylic acid **2-25** was then purified, removing the tin byproducts with a pad of KF

on top of a column of silica. The rotation of both acid derivatives resulting from the (+)-isosorbide-mediated closure as well as the (+)-xylose case resulted in a positive rotation indicating the formation of a (S) center during the 5-hexenyl cyclization. It would be interesting to study if either changing the reaction conditions, Lewis acids employed, or perhaps appending the isosorbide analog, isomannide to the chiral ester would obtain the (R) configuration. Although further experiments are possible, both carbohydrate derivatives, (+)-isosorbide and (+)-xylose, have demonstrated impressive utility as chiral templates for the intramolecular free radical cyclizations.

Conclusions

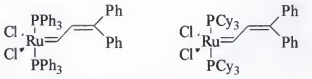
The highly oxygenated nature of carbohydrate derivatives is extremely advantageous; offering both ease in functionalization or adding appendages and providing multiple sites for Lewis acid chelation. Moreover, these moieties are commercially accessible, as well as inexpensive to purchase. The motivation of this investigation was to demonstrate the inherent potential of such molecules as chiral templates for free radical reactions, specifically a 5-exo-hexenyl radical cyclization. Both (+)-isosorbide and the monoacetonide (-)-xylose were examined. When coupled with various Lewis acids, (+)-isosorbide proved to be an effective chiral template, resulting in a distereomeric excess of 100:1 in some cases, whereas (-)-xylose demonstrated ratios of 70:1. Although the literature displays very few accounts of sugar derivatives as chiral scaffolds, it is imperitive that such studies continue and

expand in nature, fully cataloging the inherent potential of carbohydrates as chiral auxiliaries in free radical chemistry.

CHAPTER 3
RING OPENING METHASIS OF AN (+)-ISOSORBIDE FUNCTIONALIZED SUCCINIMIDE DERIVATIVE AND THE CORRESPONDING 5-HEXENYL AND 6-HEPTENYL RADICAL CYCLIZATIONS ON POLYMER SUPPORT

Introduction

During the past two decades, intense research efforts have enabled an in-depth understanding and utilization of the transition metal catalyzed olefin metathesis reaction.[57] The catalytic metal systems produced by Grubbs and Schrock have introduced practical, soluble polymers and their noted advantages as reaction carriers to synthetic chemists.[58] In particular, ring opening metathesis polymerization (ROMP), is commonly enacted by Grubbs' ruthenium-based catalysts $(Ph_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$, **3-1,** and $(Cy_3P)_2Cl_2Ru{=}CHCH{=}CPh_2$, **3-2**, (Figure 3-1).[59] The various electron-withdrawing ligands on the metal center activate the bound



3-1 **3-2**

Figure 3-1. Grubbs' ruthenium olefin metathesis catalyst.

alkylidene for coordination to the electron rich double bond of the strained cyclic olefin. The formation of a metallo-cyclobutane, resulting from a [2+2]-like cycloaddition of the alkylidene and the cyclic substrate's double bond, is typically considered an energetically unfavorable process, due to the formation of a small, strained cyclic adduct (See Figure 1-10 in Chapter 1). However, the release of the inherent strain in the norbornene system provides the energy needed to surmount this activation barrier. Once formed, the metallocycle undergoes a retro [2+2] addition to produce a molecule of ethylene, (the release of a small molecule being entropically favored), and a new metal alkylidene. This stitching process is continued, potentially creating high molecular weight polymers, until the reaction is quenched with a capping agent.

There is definite momentum within the synthetic community to explore carbon-carbon bond forming processes within a soluble polymer environment.[36] This movement is driven by the multitude of benefits attained by polymer-supported chemistry, namely, ease in product purification and isolation. Our investigations were further motivated by an alleviation of tin by-product removal from the tributyltin hydride-mediated radical cyclization. The difficulty of tin removal is considered the nemesis of tin methodology, which hinders its use and application to pharmaceutical syntheses.

In order to attain stereoselectivity in soluble polymer-supported reactions, the attachment of chiral auxiliaries to soluble polymer precursors has been explored. Polymer-bound chiral auxiliaries are of particular importance as they can lead to asymmetric reactions with facile recycling of the auxiliary by simple filtration. For

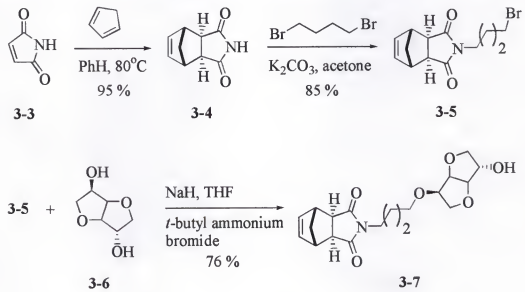
instance, the popular Evan's oxazolidinone, one of the most versatile and successful chiral scaffolds, has been appended to an insoluble polymer backbone.[31,32,33] Moreover, a manganese(III) salen complex used for asymmetric epoxidation has also been mounted on various insoluble and soluble supports.[34] The demands of high stereoselectivity within the combinatorial/drug discovery effort require investigators to seek new means of incorporating asymmetry into their polymer-supported transformations.

Our studies on stereoselective 5-exo-hexenyl radical cyclizations were first initiated within traditional liquid phase chemistry parameters. A survey of various solvent systems, radical initiators, chiral auxiliaries, and Lewis acids resulted in a highly stereo-differentiating, optimized protocol. The adaptation of this chemistry to polymer-support was modeled after Kiessling's norborene imide.[39] This polymerization precursor, despite many heteroatoms and tethered carbohydrate derivatives, polymerized smoothly with Grubbs' catalyst to give high molecular weight products. These results illustrated promise for our studies, which were to append a sugar derivative, (+)-isosorbide, to a similar system. The work herein discusses the first examples of stereoselective radical cyclizations on a metathesis support.

Synthesis of Methodology Precursors

The cyclization methodology precursor was incorporated into the polymer backbone before polymerization of the norborene system. The strained norborene

adduct was formed by the Diels Alder reaction of **3-3** and cyclopentadiene (Scheme 3-1). The inherent strain in the norborene ring is responsible for driving the ring opening metathesis polymerization (ROMP). Commercially available malimide **3-3** was combined with freshly distilled cyclopentadiene and heated under reflux conditions at 80°C overnight. ^{1}H NMR studies indicated the presence of only one isomer, the exo cyclized adduct. The tri-cyclic adduct **3-4** was functionalized by deprotonation of the imide proton by potassium carbonate in the presence of 1,4-dibromobutane. The remaining halide was displaced with (+)-isosorbide in a

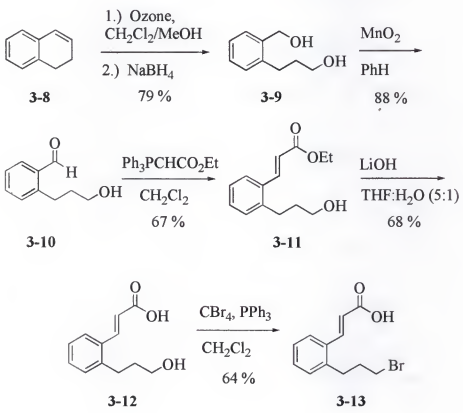


Scheme 3-1

Williamson ether synthesis, yielding the desired product **3-7** in 76 % yield. Polymerization of this moiety was attempted at this point to ensure this highly oxygenated molecule could indeed polymerize in the presence of Grubbs' ruthenium catalyst. Ether **3-7** did polymerize in 80 % yield, although the reaction needed to stir

under an oxygen-free environment for two days before any high molecular weight polymer was observed. The synthesis of the methodology precursor was continued with a 1,3-dicyclohexylcarbodiimide (DCC) coupling of the free alcohol on ether **3-7** and carboxylic acid **3-13** or **3-20**.

Acid **3-13** was constructed initially from 1,2-dihydronapthalene (**3-8**) which was purchased from Aldrich Chemical Co. This substrate was subjected to ozonolysis conditions immediately followed by reductive work-up with sodium borohydride (Scheme 3-2). Diol **3-9** was selectively oxidized with manganese

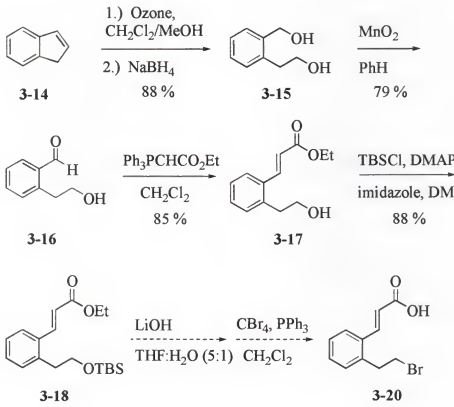


3-8 **3-9** **3-10** **3-11** **3-12** **3-13**

Scheme 3-2

dioxide, yielding the benzaldehyde derivative **3-10** in 70 % overall yield. A Wittig reaction was performed on the substrate **3-10**, providing α,β-unsaturated ethyl ester **3-11**. The ester was saponified with lithium hydroxide in a $THF:H_2O$ (5:1) mixture. Carboxylic acid/alcohol **3-12** was converted to the corresponding bromide **3-13**, using traditional means with carbon tetrabromide and triphenylphosphine. This acid precursor will allow study of the ROMP polymer supported 6-heptenyl cyclizations.

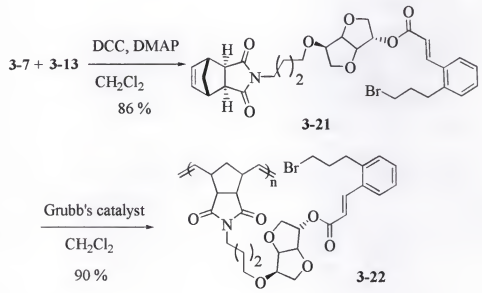
Carboxylic acid precursor **3-20** would have been assembled in an analogous fashion varying only in the starting substrate, however, the lithium hydroxide saponification reaction yielded the cyclization adduct of an intramolecular Michael addition of the free-hydroxy group. Presently, many various alcohol protecting groups, such as *t*-butyldimethyl silyl ether **3-18,** are being explored that will not only



3-14 **3-15** **3-16** **3-17** **3-18** **3-20**

Scheme 3-3

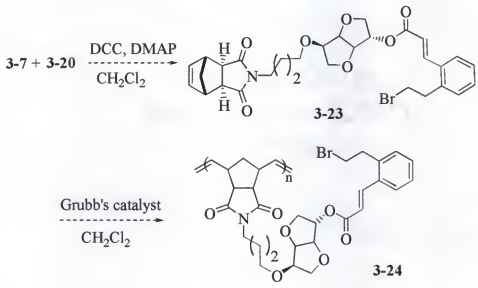
be resilient to the saponification conditions, but will also be easily removable after the carboxylic acid functionality is achieved. The unprotected compound **3-17** has been subjected to both basic (LiOH) and acidic (TFA) saponification conditions. Some protecting groups that are being explored are *t*-butyldimethyl silyl, *t*-butyldiphenyl silyl, and methylmethoxy ethers. Once obtained, the bromide precursor **3-20** will be used in the polymer-supported 5-hexenyl radical cyclizations (Scheme 3-3).



Scheme 3-4

After DCC coupling of ether **3-7** with acid **3-13** (Scheme 3-4) and the coupling of ether **3-7** with acid **3-20** (Scheme 3-5), polymerization of the succinimide derivatives **3-21** and eventually **3-23** was explored. Although the reaction times were lengthy, spanning from 2 to 3.5 days, relatively high molecular weight polymers were isolated. The brown solid was precipitated from methanol at ambient temperature

and was washed several times with excess solvent to remove unwanted by-products. The polymer was dried extensively on a high vacuum pump before the radical cyclization reactions were attempted. Because of the solubility of



Scheme 3-5

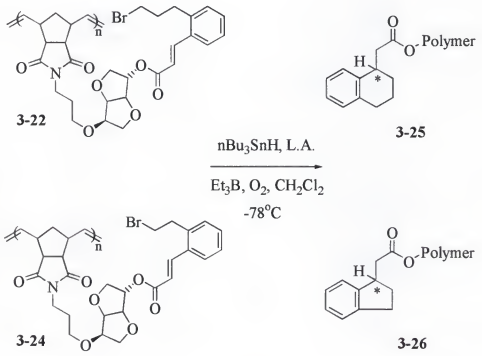
the polymers generated, ^{1}H NMR techniques could be employed to observe reaction completion and success. Moreover, GPC analysis was obtained to elucidate the extent of polymerization of such a highly oxygenated substrate. Such analysis indicates an average molecular weight of 8,500 and a polydispersity of 1.3 for ROMP polymer **3-22**.

Results and Discussion

Employing the insight gained from our previous success with 5-exo radical cyclizations in a traditional liquid phase manifold, less effort was put forth exploring

solvent systems, temperatures, and radical initiators. However, it was our goal to emulate, if not surpass, the high stereoselectivity observed in those past studies. Similar Lewis acids were used, such as magnesium bromide etherate, zinc chloride, diethylaluminum chloride and lanthanide, ytterbium(III) triflurometha ne sulfonate. Because soluble polymers behave much like normal solution phase organic reactions, very little variance to our original procedure was needed. The only precaution taken, aside from the exclusion of moisture and oxygen, was the thorough drying of the polymer-supported precursor before the cyclization reactions were carried out. The polymer-supported 6-heptenyl radical closure followed the same procedure.

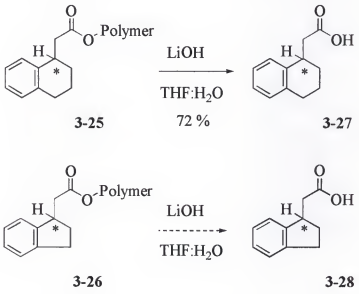
The polymer-supported cyclization precursor was dissolved to make a 0.5 M solution in methylene chloride. The desired Lewis acid was added and the reaction



Scheme 3-6

flask was purged with argon. The Lewis acid was stirred at ambient temperature for ten minutes to allow metal/sugar complexation, after which the reaction was cooled to -78°C. Triethyl borane (1 M solution in hexane) was utilized as the radical initiator. Tributyltin hydride was the radical propagator (Scheme 3-6). After reaction completion, usually 10 hours with oxygen addition every hour, the mixture was simply poured into ambient temperature methanol and filtered. The precipitate was washed with excess solvent to remove any tin residue. The collected polymer was subjected to immediate saponification conditions (Scheme 3-7), so that enantiomeric excess could be studied by chiral HPLC (a (S)-*tert*-leucine (R)-1-(α-naphthyl) ethylamine column by Phenomenex was used).

As observed in earlier studies, (+)-isosorbide illustrates a high affinity for Lewis acids, as demonstrated by a substantial increase in the diastereoselectivity for



Scheme 3-7

the cyclization. This high selectivity was justified by the highly oxygenated surface of the sugar, providing many sites for metal chelation. Thus, avidity, rather than

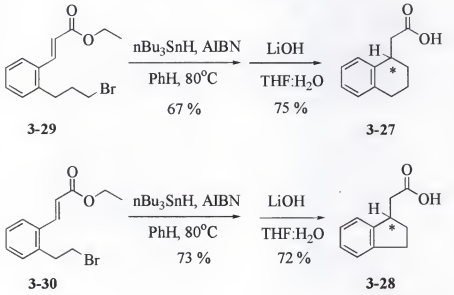
Table 3-1. Enantiomeric excess of the polymer-supported (+)-isosorbide mediated 6-heptenyl radical cyclization.

	Radical Initiator	***T*, °C**	**Solvent System**	**Lewis Acid**	**% e.e**	**Yield**
1*	AIBN	80	Benzene	N/A	0	87
2	Et_3B, O_2	0	CH_2Cl_2	N/A	40	84
3	Et_3B, O_2	-78	CH_2Cl_2 / ether	$MgBr_2$ OEt_2	86	84
4	Et_3B, O_2	-78	CH_2Cl_2 / THF	$ZnCl_2$	>99	80
5	Et_3B, O_2	-78	CH_2Cl_2	$Yb(OTf)_3$	75	72

* racemate (cyclization of an ethyl ester)

affinity for a Lewis acid is the probable cause for the efficient transfer of asymmetry. Analogous to the previous liquid phase investigation, the (+)-isosorbide functionalized cyclization precursor illustrated a preference for zinc chloride and magnesium bromide etherate in the 6-heptenyl radical closure. Although ytterbium triflate and magnesium bromide etherate were successful in enhancing the stereoselectivity of the cyclization with enantiomeric ratios of 75%, and 86% respectively, >99% enantiomeric excess was achieved with zinc chloride (Table 3-1). Diastereomeric excesses of >100:1 were observed for both zinc and magnesium for the liquid phase studies.

The racemate for both the 6-heptenyl and 5-hexenyl radical cyclization adducts were synthesized independently. The analogous ethyl esters **3-29** and **3-30** were constructed for both precursors and cyclized at 80°C with azobisisobutyronitrile (AIBN) and tributyltin hydride (Scheme 3-8). Saponification of the ester followed, allowing the enantiomeric excess of the radical closure to be analyzed. Cyclized adducts **3-27** and **3-28** were then used for a reference in the chiral HPLC work. Both



Scheme 3-8

chromatograms for the racemate reference showed a 50:50 mixture of the two enantiomers. At times, co-injections with this racemic mixture were used to fully establish enantiomeric purity.

Conclusions

The appendage of (+)-isosorbide onto a norborene imide ROMP precursor resulted in a high molecular weight polymer with a potential chiral auxiliary mounted on every monomer unit. The ability of the derivatized sugar to control the selectivity of both a 5-exo hexenyl and 6-heptenyl radical cyclization has been demonstrated. Moreover, various Lewis acids in combination with the carbohydrate auxiliaries provided enantiomeric excesses of >99%. The full benefit of the polymer-supported chemistry was illustrated by facile removal of resilient tin by-products by simply precipitating the polymer and washing with excess methanol. The ease in purification gained by the polymer-support methodology in tandem with high stereoselectivity resulting from Lewis acid chelation of highly oxygenated carbohydrate scaffolds was demonstrated by a 6-heptenyl and soon following 5-hexenyl radical closures on ROMP polymers.

CHAPTER 4
A HETEROATOM DERIVATIVE OF THE 5-EXO HEXENYL RADICAL CYCLIZATION IN THE PRESENCE OF VARIOUS LEWIS ACIDS AND AN (+)-ISOSORBIDE CARBOHYDRATE CHIRAL AUXILIARY

Introduction

The free radical cyclization methodology is often employed to construct carbocycles, commonly the cyclopentyl structure, under mild, neutral conditions with high conversion to product. However, the assemblage of heterocycles, a common skeleton in natural product synthesis, can also be accomplished by free radical transformations. The tin hydride method has been used extensively for the construction of oxygen-containing ring systems. Interestingly, when oxygen or nitrogen resides in the 3-position of 5-hexenyl radical closures, there is more than a 10 fold increase in the rate of cyclization.[60] The accepted explanation for this accelerated rate is that the C-O bonds are shorter and the C-O-C bond angle is smaller, both characteristics lending to more overlap during the transition state of the closure. Because of this acceleration, hydrogen transfer can no longer compete with the rate of cyclization, often resulting in oxygen and nitrogen heterocycles exclusively.

The regioselectivity of oxygen containing radical closures is augmented as well. Because the 6-heptenyl closure does not benefit from this increased overlap in the transition state, the 5-exo-hexenyl radical cyclization is the only product

observed.[61] Radical additions to alkenes are faster than comparable additions to alkynes, but the rate of 5- vs. 6- membered ring radical closures is often still retained, regardless of the level of unsaturation.

The popular conversion of an allylic alcohol, a readily available precursor, to γ-lactones has been applied to many synthetic strategies. Perhaps most notable is the work done by Stork with his (+)-prostaglandin $F_{2\alpha}$ synthesis,[62] Holton's assembly of taxusin,[63] and Pattenden's ginkgolide ring systems.[64,6] Holten's construction of taxusin, a four-step procedure of alkylation, cyclization, deprotection and oxidation

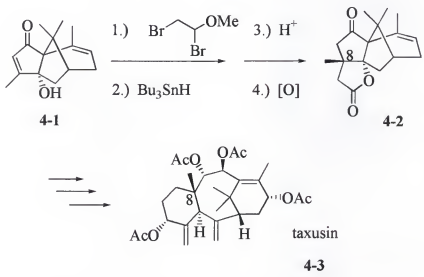


Figure 4-1. Holten's free radical approach to taxusin.

yield an important, oxygenated ring intermediate (Figure 4-1). The conversion of the tertiary alcohol to the corresponding lactone was achieved in an impressive 82% yield over four steps.[63] Although the structural skeleton of the lactone is difficult to find in the final target, the configuration of the tertiary alcohol was used to set the stereochemistry of the methyl group at C8 in taxusin. The ability to construct

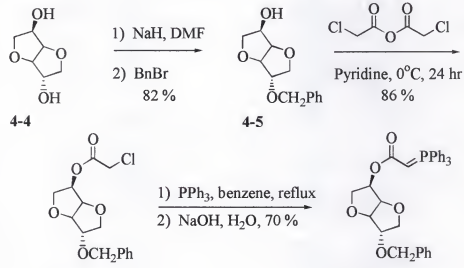
complex, sterically hindered bonds, as well as heterocyclic structures, through a mild and neutral process, makes tributyltin hydride-mediated radical cyclizations a powerful tool for synthetic chemists.

The sophistication of Stork's elegant methodology of transforming allylic alcohols to γ-lactones can be enhanced by the addition of asymmetric induction, lending to a stereoselective process. This can be achieved through either an appended chiral auxiliary or a designer chiral Lewis acid, both of which have been investigated only minimally in this area.

Due to our recent success with the carbohydrate derivative, (+)-isosorbide, as a chiral template for 5-exo-hexenyl radical closures, an expansion of this methodology to heterocyclic moieties was a logical next step. Because of the prevalence of oxygenated heterocycles in natural products, a need exists for stereoselective cyclizations, tolerant of the many complex and interesting functionalities common on such synthetic precursors. A bromoether that functioned as the cyclization precursor was constructed and subjected to tin-mediated free radical conditions. A survey of Lewis acids, radical initiators, temperature and solvent, analogous to the original investigation of the (+)-isosorbide carbohydrate auxiliary, 5-exo-hexenyl radical cyclization, ensued. Extremely high levels of enantioselectivity were observed in this radical reaction. The results of this study are discussed herein.

Synthesis of Methodology Precursors

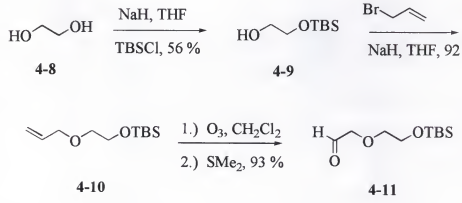
The methodology precursor was constructed in a convergent fashion, where an (+)-isosorbide Wittig reagent was synthesized independent of a TBS (*t*-butyldimethyl silyl) protected aldehyde. The carbohydrate-derived Wittig reagent



4-4 **4-5** **4-6** **4-7**

Scheme 4-1

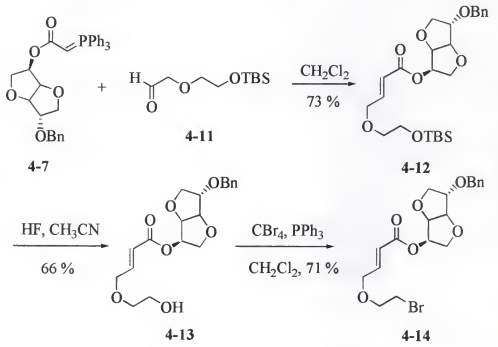
was synthesized in three steps from commercially available (+)-isosorbide **4-4**, as illustrated in Scheme 4-1. Monobenzylation of (+)-isosorbide **4-4** was achieved by



4-8 **4-9** **4-10** **4-11**

Scheme 4-2

deprotonation using sodium hydride, followed by trapping of the alkoxide anion with benzyl bromide in 82 % yield.[53] The remaining hydroxyl functionality was converted to chloroester **4-6** using chloroacetic anhydride in pyridine and chloroform. Transformation to the corresponding ylide **4-7** was achieved by heating **4-6** in the presence of triphenylphosphine followed by deprotonation by sodium hydroxide. Purification of **4-7** was achieved through a series of extractions. Aldehyde **4-11** was derived from readily available ethylene glycol (Scheme 4-2). Ethylene glycol **4-8** was first monoprotected with *tert*-butyldimethylsilyl (TBS) chloride. The monoalcohol **4-9** was etherified via a Williamson ether synthesis using sodium hydride and allyl bromide. The allyl ether **4-10** was subjected to ozonolysis conditions to produce aldehyde **4-11** in 86 % overall yield.

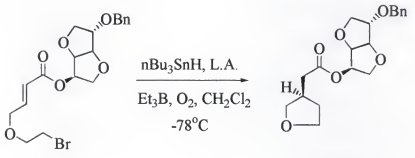


Scheme 4-3

A Wittig coupling of **4-7** and **4-11** yielded α,β-unsaturated chiral ester **4-12** in 73 % isolated yield. The silyl protecting group was removed with a 49% HF solution. Functional group transformation of alcohol **4-13** to bromide **4-14** was accomplished using carbon tetrabromide, triphenylphosphine in methylene chloride (Scheme 4-3).

Results and Discussion

Once the unsaturated bromoester of the heteroatom derivative had been synthesized, various reaction conditions for the 5-hexenyl radical cyclization were explored. Free radical conditions were utilized which were successful in the

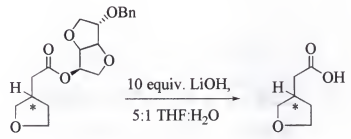


4-14 **4-15**

Scheme 4-4

analogous case of the carbo-5-exo-hexenyl cyclization (Scheme 4-4). Triethyl borane and oxygen were employed as the radical initiators. Methylene chloride was always used as the solvent of choice, although an ether or tetrahydrofuran co-solvent was implemented when Lewis acid (L. A.) solubility became an issue (i.e. $Yb(OTf)_3$, $ZnCl_2$). In this study, only enantiomeric excess was analyzed, therefore the cyclized

adduct was immediately saponified forgoing purification of the intermediate cyclized ester (Scheme 4-5). The tin-byproducts and impurities were removed by



4-15 **4-16**

Scheme 4-5

manipulating the pH of the extraction, retrieving the desired cyclized carboxylic acid **4-16** at pH 2. The enantiomeric ratio was determined by a (S)-*tert*-leucine (R)-1-(α-naphthyl)ethylamine chiral HPLC column by Phenomenex. The results of the

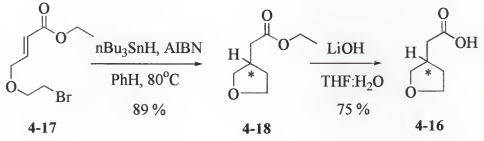
Table 4-1. Enantiomeric excess of the (+)-isosorbide mediated 5-hexenyl radical heteroatom cyclization.

	Radical Initiator	***T*, °C**	**Solvent System**	**Lewis Acid**	**% e.e**	**Yield**
1*	AIBN	80	Benzene	N/A	0	90
2	Et_3B, O_2	0	CH_2Cl_2	N/A	2	82
3	Et_3B, O_2	-78	CH_2Cl_2 / ether	$MgBr_2$ OEt_2	>99	80
4	Et_3B, O_2	-78	CH_2Cl_2 / THF	$ZnCl_2$	>99	85
5	Et_3B, O_2	-78	CH_2Cl_2	$Yb(OTf)_3$	56	73
6	Et_3B, O_2	-78	CH_2Cl_2	Et_2AlCl	51	78

* racemate (cyclization of an ethyl ester)

cyclization are illustrated in Table 4-1. For a standard, an ethyl ester was cyclized under radical cyclization conditions, saponified and injected onto the HPLC column. Run 1 is illustrative of the racemate mixture (Scheme 4-6). The S isomer was preferred in all Lewis acid mediated cyclizations. Elucidation of the center was accomplished by comparison with the literature rotation of both the S and R enantiomers.[65]

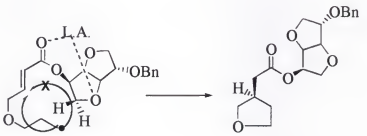
The high level of asymmetric induction observed during this radical cyclization was unexpected. Initially, we had attributed the success of the earlier all-



Scheme 4-6

carbon 5-exo-hexenyl closure to the steric bulk of the adjacent benzene ring, in addition to the Lewis acid chelate with the carbohydrate auxiliary. The predominant source of stereoselectivity was, therefore, ascribed to steric mass. However, the heteroatom precursor molecule had only an oxygen atom for steric bulk to discern one radical approach from another. Instead of utilizing steric influences, it was our hope, in the design of the heteroatom precursor, to take advantage of the oxaphilicity of certain Lewis acids, such as magnesium, zinc and aluminum, and incorporate the lone pair of a heteroatom in a position where further metal chelation was possible. In

fact, if the ether oxygen of the cyclization precursor is complexed to a Lewis acid, a six-membered chelate is formed between that oxygen, the metal, and the lone pair on the carbonyl of the ester. However, it is difficult to envision and predict how the asymmetry of the chiral auxiliary is connected to the complexed lone pair of the ether oxygen. It could be postulated that a multi-metal center involving both the ether oxygen and the sugar derivative is responsible for the observed stereo-differentiation during the cyclization process. Several possibilities for a metal complex exist, one such model is illustrated in Scheme 4-7.



4-16 **4-15**

Scheme 4-7

Conclusions

The highly oxygenated nature of carbohydrate derivatives is extremely advantageous; offering both ease in functionalization or adding appendages and providing multiple sites for Lewis acid chelation. The motivation of this investigation was to demonstrate the inherent potential of such molecules as chiral templates for a free radical heteroatom cyclization, specifically a 5-exo-hexenyl radical closure. When coupled with various Lewis acids, particularly magnesium

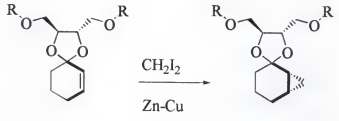
bromide etherate and zinc chloride, (+)-isosorbide proved to be an effective chiral template, resulting in an enantiomeric excess of >99%. A viable expansion of earlier studies on carbohydrate chiral auxiliaries and 5-exo hexenyl radical cyclizations to heteroatom cyclizations has been enacted. Again, (+)-isosorbide has demonstrated a definite preference for the chelating abilities of magnesium and zinc Lewis acids, exhibiting high stereoselectivity in excess of 99% e.e. Because of the success of this study, an extrapolation to nitrogen containing heterocyclic compounds should be next pursued. Moreover, the results recently obtained for radical cyclizations on a ROMP polymer (Chapter 3) also present a potential application to this oxygenated cyclization reactions.

CHAPTER 5
THE UTILIZATION OF A TARTRATE DERIVATIVE AS A NONCROSSLINKED, POLYSTYRENE LINKER

Introduction

Most synthetic routes require protection of reactive carbonyl functionalities before a chemical transformation of another group can be attempted. Perhaps one of the most commonly employed carbonyl protecting groups is an acyclic or cyclic acetal or ketal. This protecting group is advantageous because it is resistant to basic and nucleophilic conditions, yet is easily removable in acidic medium.[66]

Homochiral acetals and ketals have been readily investigated because of their ability to act as a protecting group and to induce asymmetry in synthetic

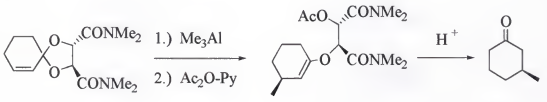


5-1 **5-2**

Scheme 5-1

transformations. This bifunctional methodology has been exploited through such transformations as cyclopropanations,[67,68,69] epoxidations,[70] and alkylations.[71,72] For example, chiral ketals of α,β-unsaturated carbonyl compounds are commonly used to furnish diastereoselective Simmons-Smith cyclopropanation reactions (Scheme 5-1).[73,74] The appendage of a chiral diol through a ketal linkage permits the conversion of a double bond to the corresponding cyclopropane ring in a stereoselective fashion. Mash and co-workers suggest that specific chelation of the metal reagent to the highly oxygenated ketal moiety is responsible for the observed stereoselectivity.[68,69] Interestingly, the ring size and the substituents on the starting enone usually do not affect the diastereoselectivity of the reaction.[73]

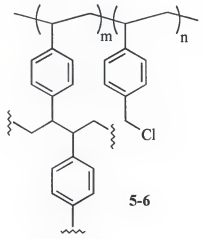
The use of homochiral ketals can be further extended with S_N' reactions with organometallic reagents. For instance, Yamamoto and coworkers have demonstrated a facile route to optically active β-substituted ketones *via* stereoselective conjugate addition of organoaluminium compounds to chiral ketal **(5-3)** (Scheme 5-2).[72] This reaction proves to be equally versatile when acyclic, as well as cyclic substrates, are equally employed.



5-3 **5-4** **5-5**

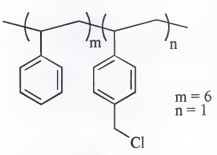
Scheme 5-2

There is a significant amount of valuable homochiral ketal chemistry that can be applied to polymer-supported systems. The appendage of traditional liquid phase chemistry to a polymer backbone offers many synthetic advantages such as alleviating tedious purification and by-product removal (i.e. tin pollution). Janda and co-workers first demonstrated the utility of a non-crosslinked polystyrene polymer with his convergent synthesis of Prostaglandin E_2.[75] A non-cross-linked polystyrene support was selected over the more traditional insoluble supports because of the solubility properties. The ultimate difference in the solubility of the two polymers results from the linking of the polymer backbone into a rigid framework, affording a cross-linked polymer. This rigidity prevents solvation of the polymer, allowing the solid phase resin to provide an insoluble solid surface for reactions to occur. Non-



5-6

Cross-linked Polymer
Solid Phase Organic Chemistry (SPOC)



5-7

Non-Cross-linked Polymer
Liquid Phase Organic Chemistry (LPOC)

Figure 5-1. An illustration of the rigid cross-linked polymer vs. the flexibile non-cross-linked polymer.

cross-linked polystyrene has a single, linear backbone, where the repeat monomer is not connected to other segments of the polymer framework. This type of polymer chain increases solvation and thus, traditional liquid phase chemistry is possible (Figure 5-1).

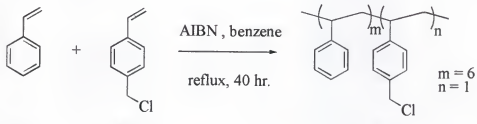
A non-crosslinked polystyrene polymer support was developed by Merrifield in the 1970s for peptide synthesis, however, its application to standard organic synthesis has not been studied in detail.[35] Researchers have found that the rate of coupling reactions for the soluble non-crosslinked polymer is on the same order of magnitude as classical liquid phase peptide synthesis, translating to a reaction rate 100 times greater than common insoluble solid phase reactions.[35] Other merits of the non-crosslinked polystyrene support (NCPS) polymer include: (1) inexpensive preparation; (2) solubility in common organic solvents (i.e. ethyl acetate, benzene, chloroform, methylene chloride, tetrahydrofuran), additionally, NCPS is insoluble in methanol and water, thereby, facilitating purification of reaction intermediates; (3) polymer bound substrates can be analyzed by ^{1}H NMR spectroscopy without cleavage from the polymer support; and (4) the amount of polymer loading can be controlled.[75]

A new synthetic methodology, involving attachment of a homochiral diol to a soluble, non-crosslinked polystyrene polymer support, was the subject of our investigations. A chiral diol, derived from diethyl-L-tartrate (**5-12**), mounted on the polymer support was reacted with various carbonyl functionalities in a preliminary study. The carbonyl compounds were removed with optimized hydrolysis conditions in modest to high yields. After the verification that traditional organic chemistry

could occur on the NCPS medium, our efforts turned to the exploitation of the inherent chirality of the diol. It was our intention to perform an asymmetric Grignard, and thus the first chiral reaction on a non-crosslinked polystyrene support.

Optimization of the Non-Crosslinked Polystyrene Support

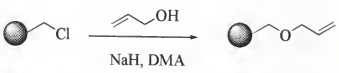
A study was conducted to explore the maximum loading capacity of this soluble polymer. The reaction (Scheme 5-3) was manipulated, varying the vinyl



5-8 **5-9** **5-10**

Scheme 5-3

benzyl chloride stoichiometry to incorporate more displacement sites into the polymer backbone. Initially, Janda and co-workers utilized 0.3 mmole/g, or a 3% loading capacity polymer for their total synthesis of prostaglandin $F_{2\alpha}$.[75] Although this



5-10 **5-11**

Scheme 5-4

loading capacity was sufficient for their work, our efforts focused on maximizing the amount of loading sites in the produced polymer. By augmenting the loading capacity of the polymer, an increase in the density of reactive sites was observed, therefore, allowing the use of less polymer in reactions. The use of less support in the reaction sequence makes this methodology more applicable to industrial processes.

The non-crosslinked polystyrene polymers were synthesized with varying equivalence of vinyl benzyl chloride (VBC). The resulting polymers were then reacted with allyl alcohol (Scheme 5-4) to obtain the loading capacity of the soluble support and the loading efficiency of the displacement. Through ^{1}H NMR integration analysis, the loading percentage of VBC and the efficiency of the displacement were calculated.

Run	Loading Capacity	Styrene (equiv.)	VBC (equiv.)	Chloro-methyl product	Alcohol Displacement	Allyl Alcohol
a	3 %	32	1	5-10 a	100 %	5-11 a
b	15 %	6.5	1	5-10 b	93 %	5-11 b
c	27 %	10.7	3.3	5-10 c	92 %	5-11 c
d	33 %	2	1	5-10 d	100 %	5-11 d

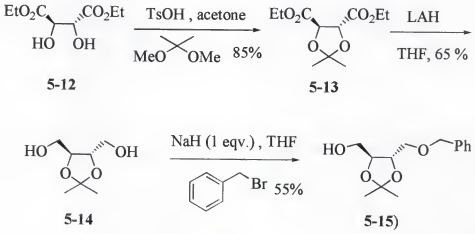
Table 5-1

It was determined from these studies that a 33% loading capacity would work most efficiently in the studies that follow. This 33% limit incorporates the maximum number of loading sites into the polymer backbone, while keeping some manageability with the material created. For example, as the loading capacity

increased above 33%, the precipitation of the polymer in cold methanol became problematic.

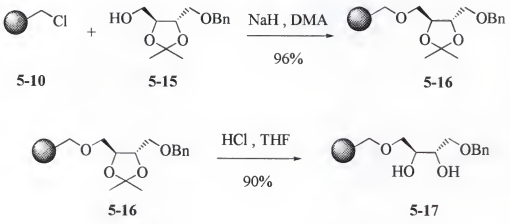
Synthesis of Methodology Precursors

The non-crosslinked polystyrene polymer was synthesized according to Janda (Scheme 5-3).[75] The percentage of reactive sites in the polystyrene polymer was determined *via* ^{1}H NMR integration of the benzyl chloride protons. The soluble polymer limits the full scope of the ^{1}H NMR because the spectrum is masked in the aryl and alkyl regions by the dominating influence of the polymer backbone. Despite this caveat, one can monitor the central region of the ^{1}H NMR spectra (2.5 to 6.2 ppm) for loading capacity and reaction completion. Overall, NCPS has a distinct, nondestructive advantage over the use of a solid phase resin, where cleavage of the product is required to monitor the progress of the reaction.



Scheme 5-5

The inexpensive, chiral starting material, diethyl-L-tartrate (**5-12**) was protected using 2,2-dimethoxypropane in acetone and a catalytic amount of *p*-toluenesulfonic acid to prepare acetonide (**5-13**). As demonstrated in Scheme 5-5, (-)-dimethyl-2,3-O-isopropylidene-L-tartrate (**5-13**) was reduced with lithium aluminum hydride and mono-benzylated with benzyl bromide and sodium hydride in THF. The chiral acetonide (**5-15**) was deprotonated with sodium hydride in dimethyl acetamide (DMA) and mounted onto the soluble polymer (**5-10**) *via* a Williamson ether synthesis (Scheme 5-6). Chiral acetonide (**5-16**) was isolated by simply pouring



5-10 **5-15** **5-16**

5-16 **5-17**

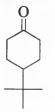
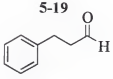
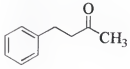
Scheme 5-6

the reaction mixture into cold methanol (-78°C), filtering and washing the white solid with excess cold methanol. Analysis of the central region of the ^{1}H NMR (2.5-6.2 ppm) revealed the presence of the adhered substrate in 96% yield. Polymer (**5-16**) was dissolved in THF and subjected to hydrolysis conditions using hydrochloric acid. Diol (**5-17**) was confirmed by a decrease in the integration of the alkyl region and a

shift of the methine proton peak. These features indicated the deprotection of the acetonide, leaving the free diol for further chemistry.

Utility of the Tartrate Moiety as a Ketal Precursor

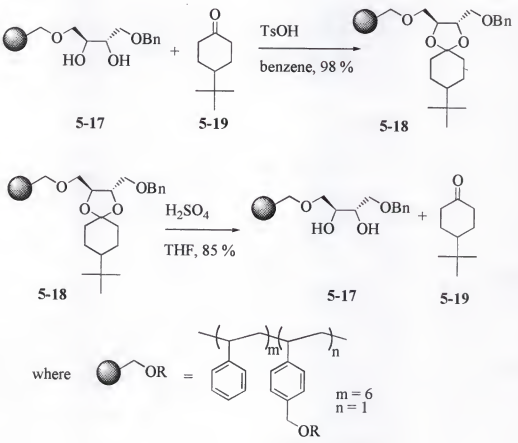
To demonstrate that traditional liquid phase chemistry could occur on our non-cross-linked polystyrene medium, several carbonyl compounds were protected

Carbonyl	Loading Percentage*	Recovery Yield
 **5-19**	98	85
 **5-20**	91	71
 **5-21**	96	84
 **5-22**	98	76

* Loading Percentages were calculated by NMR integration

Table 5-2

and deprotected with chiral diol (**5-17**), *p*-toluenesulfonic acid, and a Dean-Starke apparatus (Scheme 5-7). Ketalization yields are based on ^{1}H NMR integration, whereas recovery yields are determined by isolated product. As demonstrated in Table 5-2, both reaction yields and reaction times reflect that of traditional liquid phase chemistry. In all the examples, ketalization of the carbonyl functionality was



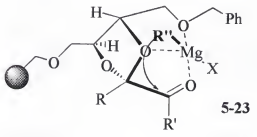
Scheme 5-7

smooth and high yielding. The diol-mounted polymer (**5-17**) was dissolved in benzene and the carbonyl component was added. The mixture was refluxed with a Dean-Starke apparatus until the presence of water was evident. The polymer was

then precipitated in cold methanol and the ketal-mounted substrate was recovered. Hydrolysis of the ketal afforded modest yields after isolation of the original ketone or aldehyde. Nonetheless, it was evident that the traditional protecting group chemistry could be applied to this polystyrene environment with fairly good success.

An Asymmetric Grignard on Soluble Support

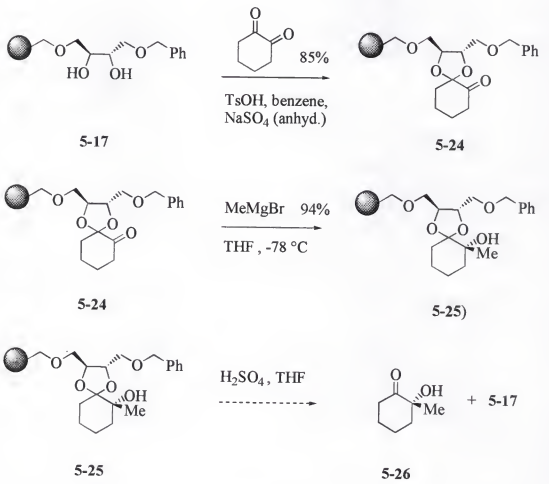
The investigation of an enantioselective Grignard reaction on the NCPS technology was explored. It was our intention to demonstrate that transfer of an alkyl group in an enantioselective fashion will react *via* a metal chelate of the oxygen rich ketal.[76] Tamura and co-workers illustrated this chemistry earlier with their chiral ketal directed, asymmetric Grignard in liquid-phase chemistry.[75] The postulated transition state (Figure 5-2) depicts a rigid chelated complex due to coordination of the carbonyl oxygen, ketal oxygen and the alkoxy substituent to magnesium. Our goal is to exploit the geometry of the chelate and force a selective alkyl transfer to one face of the ketone while in a non-crosslinked, polystyrene environment.



5-23

Figure 5-2. A possible magnesium chelate responsible for the stereoselective Grignard reaction.

Expanding on Tamura's work with Grignard reactions on chiral ketals,[76] our efforts turned to applying this useful synthetic strategy to the non-cross-linked polystyrene support. Our free diol (**5-17**) was reacted directly with a 1,2-dicarbonyl compound, specifically, 1,2-cyclohexandione. Tamura tested his methodology starting with α-hydroxy dimethylacetal, two steps to the target carbonyl molecule. In contrast, our direct ketalization produced the protected dicarbonyl in one step, ready for the enantioselective Grignard. Ketal (**5-24**) was dissolved in THF and cooled in a



5-17 **5-24** **5-24** **5-25)** **5-25** **5-26**

Scheme 5-8

dry ice/acetone bath for 10 minutes. Cautiously, Grignard reagent was added and the resulting mixture was allowed to warm to room temperature and stir overnight. Scheme 5-8 illustrates the Grignard reaction with the homochiral ketal and subsequent hydrolysis of the product off the polymer support.

After addition of the Grignard reagent, ^{1}H NMR did indicate the increased integration of the alkyl region, as well as a peak shift of the methylene adjacent to the carbonyl. Despite this success, our attempts to cleave the α-hydroxy ketone from the polymer support were fraught with difficulties. The acidity levels of the reaction were increased until the methodology became impractical, offering no applicability to the synthetic community. Moreover, intense heat, various acids (i.e. *p*-toluenesulfonic acid, sulfuric acid, trifluoroacetic acid, hydrochloric acid) and acid strengths (i.e. catalytic-12 M) were also tried, but to no avail. Only small amounts of the ketal were hydrolyzed after each attempt. It is believed by ^{1}H NMR evidence that the Grignard reaction did in fact work. However, the asymmetric nature of the reaction could not be explored due to the inability to cleave the product. Literature sources only offer minor suggestions, stating that six-membered ketals are more difficult to remove compared to other cyclic moieties.[66] Perhaps, also, the hydroxyl generated after the attack of methyl Grignard played a role in the lability of the substrate from the polystyrene backbone.

Conclusions

The non-cross-linked polymer support (NCPS) has demonstrated its ability to offer an improved and efficient liquid phase support for traditional chemistry. By mounting substrates onto this medium, purification techniques are simplified and traditional chromatography is needed only when the product is finally cleaved from the support.

The common acetal protecting group was mounted on the NCPS support. The utility of the mounted diol was demonstrated by protecting and deprotecting several carbonyl compounds. Our attempts of further extending this methodology to include the asymmetric nature of the ketal were precluded. Since solid phase technology is increasingly gaining the attention of research groups, it would benefit the investigator to focus on a NCPS support that offers all of the advantages of solid phase chemistry, yet improves the utility of solid supports by offering liquid phase reaction rates and common analytical methods such as NMR, TLC and GC.

CHAPTER 6
EXPERIMENTAL

General Methods

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrometer and are reported in wave numbers (cm^{-1}). ^{1}H Nuclear magnetic resonance spectra were recorded on a Varian Gemini-300 (300 MHz) and a Mercury-300. ^{13}C NMR spectra were recorded at 75 MHz on the same spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane as an internal standard. All mass spectroscopy was performed by the Mass Spectroscopy Service at the University of Florida Department of Chemistry. Elemental analysis was performed by Atlantic Microlab Inc. in Norcross, GA. The chiral HPLC work was performed on a 250 x 4.6mm ID (S)-*tert*-leucine (R)-1-(α-naphthyl)ethylamine chiral column by Phenomenex. A UV detector (254 nm) was used for chapter 3 studies. Chapter 4 data was collected from a RI detector. Solvents for the HPLC work included HPLC-grade methanol and water. All reactions were run under an inert atmosphere of argon using clean, dry glassware. Solvents were freshly distilled before use. All yields reported refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography.

Experimental Procedures

Monobenzylated isosorbide 2-5.[53] Sodium hydride (60% mass) (15.0 mmol, 0.6 g) was added to a flask flushed with argon. The gray powder was washed three times with pentane to remove the protective oil. A dilute solution of isosorbide **(2-1)** (13.7 mmol, 2.0 g) in DMF (30 mL) was added to the sodium hydride. The mixture was stirred for 20 minutes. Benzylbromide (14.0 mmol, 1.7 mL) was added to the reaction flask and allowed to stir for 15 hours at ambient temperature. The reaction was monitored by TLC. Workup entailed an extraction with brine and diethyl ether. The organic layer was dried with anhydrous magnesium sulfate and the solution concentrated. The product was isolated by flash chromatography with silica gel (hexane/ether 35:65), leaving a colorless, residual oil **2-5** (2.7 g, 82%).
2-5 : R_f= 0.08 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 4.6 (m, 3H), 4.25 (m, 1H), 4.1 (m, 2H), 3.85 (m, 2H), 3.5 (dd, 9.3 Hz, 1H), 2.8 (s, 1H). All spectral data is in agreement with known literature values.[53]

Chloro-esterified isosorbide 2-7.[52] The monobenzylated isosorbide **2-5** (17.2 mmol, 4.07 g) was dissolved in chloroform (80 mL). The solution was cooled to 0°C in an ice-bath and allowed to stir for 10 minutes. After addition of pyridine (60.3 mmol, 4.9 mL), the reaction was stirred at 0°C for 15 minutes. In a seperate vessel, chloroacetic anhydride (34.5 mmol, 5.9 g) was dissolved in chloroform (70 mL). This solution was added dropwise to the above reaction mixture. The reaction was stirred at room temperature for 12 hours. After consumption of starting material,

dilute HCl was added to neutralize the pH. Workup entailed an extraction with brine and chloroform. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 45:55), leaving a residual oil **2-7** (4.5 g, 84%).

2-7 : R_f= 0.46 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 1.77 (c = 2.8, chloroform); ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 5.25 (d, 3.5 Hz, 1H), 4.75 (d, 11.9 Hz, 1H), 4.67 (t, 4.6 Hz, 1H), 4.55 (d, 11.9 Hz, 1H), 4.5 (m, 1H), 4.1 (m, 5H), 3.86 (dd, 8.8 Hz, 1H), 3.65 (dd, 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) 166.3, 137.5, 128.4, 127.8, 127.7, 85.4, 80.5, 80.0, 78.8, 73.2, 72.3, 70.4, 40.5 ; IR (neat): 2877.7, 1757.8, 1174.1, 699.8 cm^{-1}; HRMS calcd for $C_{15}H_{17}O_5Cl$ 312.0764, found 312.0764; Anal. Calcd for $C_{15}H_{17}O_5Cl$: C, 57.61; H, 5.48. Found: C, 57.73; H, 5.49.

Wittig reagent 2-8. Ester **2-7** (39.4 mmol, 12.3 g) was mixed with triphenylphosphine (118.2 mmol, 31.0 g) and benzene (50 mL) and allowed to reflux for 15 hours. The resulting solution was cooled to room temperature. Benzene (20 mL) was added to the mixture to dissolve the excess triphenylphosphine. This procedure was repeated 3 times, discarding the benzene layer. Hot water was added to dissolve the salt formed in the flask. Once dissolved, 0.1 M NaOH was added dropwise until no further white ppt. was formed. More ppt. was observed upon cooling of the flask in an ice-bath for 1 hour. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was thoroughly dried by a vacuum pump to give **2-8** (17.2 g, 81%).

2-8 : R_f = 0.054 (35:65 EtOAc:Hex); [α]$^{25}_D$ = + 39.7 (c = 3.2, chloroform); ^{1}H NMR ($CDCl_3$) 7.63 (m, 5H), 7.42 (m, 10H), 7.29 (m, 5H), 5.1 (d, 12 Hz, 1H), 4.77-4.4 (m, 4H), 4.07-3.4 (m, 6H), 1.98 (d, 13 Hz, 1H); ^{13}C NMR ($CDCl_3$) 137.4, 133.4, 133.1, 132.9, 132.7, 132.5, 132.4, 131.7, 131.6, 131.56, 131.5, 131.35, 131.3, 130.1, 129.9, 128.5, 128.3, 128.2, 128.14, 128.1, 128.0, 127.9, 127.7, 127.5, 127.4, 127.3, 127.23, 127.2, 85.4, 80.5, 80.0, 78.8, 73.2, 72.3, 70.4, 69.4; IR (neat): 3048.5, 2954.5, 2355.1, 1619.3, 1434.3, 1190.4, 1108.1, 884.8, 743.8, 696.8 cm^{-1}; HRMS calcd for $C_{33}H_{31}PO_5$ 538.1909, found 538.1987.

Lactone 2-10.[77] Isochroman **2-9** (75 mmol, 10 g) was dissolved in freshly distilled methylene chloride (150 mL) and stirred under argon. To the solution, 1 equiv. of pyridinium chlorochromate (PCC) (75 mmol, 16 g) was added. After the mixture was stirred for 2 hours at reflux, 2 more equiv. of PCC were added. The reaction was monitored by TLC. Upon completion, the reaction was cooled and filtered through a plug of silica. The product was isolated by flash chromatography on silica gel (hexane/ether 70:30), leaving a residual oil **2-10** (7.9 g, 72%).

2-10 : R_f = 0.47 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 8.1 (d, 7.8 Hz, 1H), 7.5 (m, 1H), 7.4 (m, 1H), 7.3 (m, 1H), 4.5 (t, 5.9 Hz, 2H), 3.1 (t, 5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) 164.7, 139.3, 133.3, 129.7, 127.2, 127.0, 124.8, 67.0, 27.3, 28.0; IR (neat): 2899.5, 1725.1, 1605.2, 1294.6, 1120.3, 744.3 cm^{-1}; HRMS calcd for $C_9H_8O_2$ 148.0652, found 148.052; Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.73; H, 5.51.

Lactol 2-11. Lactone **2-10** (47.8 mmol, 7.1 g) was dissolved in methylene chloride (96 mL) and cooled in a round bottom flask to –78°C in a dry ice/acetone bath. Diisobutylaluminium hydride (DIBAL) (47.8 mmol, 6.8 g) was added to the reaction dropwise. The reaction was monitored by TLC. The reaction mixture was quenched with 5 mL of methanol at –78°C. The mixture was then poured into a flask and stirred rapidly with Rochelle's salt. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate. The solution was concentrated and further purified by flash chromatography on silica gel (hexane/ether 55:45), leaving a crystalline solid (mp 73-74 °C) **2-11** (6.1 g, 84.5%).

2-11 : R_f= 0.47 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 7.3 (m, 1H), 7.25 (m, 2H), 7.14 (m, 1H), 5.9 (d, 5.4 Hz, 1H), 4.2 (ddd, 3.7 Hz, 3.5 Hz, 3.7 Hz, 1H), 3.95 (dddd, 2.7 Hz, 1H), 3.0 (m, 2H), 2.7 (dt, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) 135.0, 134.1, 128.5, 128.2, 127.3, 126.5, 91.5, 58.4, 28.0; IR (nujol): 3356.1, 2932.1, 1724.1, 1606.3, 1459.1, 740.6 cm^{-1}; HRMS calcd for $C_9H_{10}O_2$ 150.0681, found 150.0681; Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found : C, 72.04; H, 6.60.

Aldehyde 2-12. Lactol **2-11** (33 mmol, 5.0 g) was dissolved in DMF (0.5 M) in a round bottom flask. Imidazole (167 mmol, 11.3 g) and DMAP (3.3 mmol, 0.41 g) were added to the reaction mixture. The solution was degassed with argon for twenty minutes at room temperature. Slowly, *t*-butylchlorodiphenylsilane (59.4 mmol, 16.3 g) was added dropwise and the resulting solution was allowed to stir overnight (12 hours). Workup entailed an extraction with brine and diethyl ether. The organic

layer was dried with anhydrous magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 65:35), leaving a residual oil **2-12** (10.3 g, 80%).

2-12 : R_f= 0.84 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 10.2 (s, 1H), 7.5 (m, 4H), 7.33 (m, 10H), 3.9 (t, 6.36 Hz, 2H), 3.3 (t, 6.36 Hz, 2H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) 192.3, 135.5, 133.5, 133.4, 132.1, 131.1, 129.6, 127.7, 127.6, 126.8, 64.6, 35.2, 26.7, 26.5, 19.0; IR (neat): 3073.7, 2855.8, 1692.3, 1599.7, 1109.3, 1016.7, 744.2, 700.6 cm^{-1}; HRMS calcd for $C_{25}H_{28}SiO_2$ 388.1859, found 388.1859.

Isosorbide Wittig adduct 2-13. Aldehyde **2-12** (10.3 mmol, 4.0 g) and Wittig reagent **2-8** (20.6 mmol, 11.1 g) were combined in a oven dried flask and dissolved in freshly distilled methylene chloride (1 M). The reaction was stirred for 15 hours at room temperature. After completion of the reaction, the solvent was evaporated and the remaining residue was purified by column chromatography (hexane/ether 50:50) to give **2-13** (3.1 g, 46%).

2-13 : R_f= 0.64 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = +34.8 (c = 1.3, chloroform); ^{1}H NMR ($CDCl_3$) 8.1 (d, 15.8 Hz, 1H), 7.55 (m, 5H), 7.35 (m, 14H), 6.32 (d, 15.8 Hz, 1H), 5.3 (d, 3.5 Hz, 1H), 4.79 (d, 12 Hz, 1H), 4.7 (t, 4.3 Hz, 1H), 4.58 (d, 11.8 Hz, 1H), 4.54 (s, 1H), 4.18 (dd, 3.7 Hz, 1 H), 4.1 (m, 2H), 3.9 (dd, 6.6 Hz, 1H), 3.8 (m, 2H), 3.68 (dd, 8.2 Hz, 1H), 3.02 (t, 6.6 Hz, 2H), 0.97 (s, 9 H); ^{13}C NMR ($CDCl_3$) 165.8, 143.5, 139.1, 137.6, 135.4, 133.3, 131.1, 130.0, 129.4, 128.4, 127.9, 127.5, 126.7, 126.3, 118.5, 85.9, 80.5, 79.0, 78.5, 73.8, 72.4, 70.2, 64.5, 35.9, 26.8, 26.7, 19.0; IR (neat): 3063.1, 2931.1, 2858.0, 1716.0, 1632.8, 1167.6, 1106.6, 702.6 cm^{-1}; HRMS calcd for

$C_{40}H_{44}SiO_6$ 648.2907, found 648.2907; Anal. Calcd for $C_{40}H_{44}SiO_6$: C, 74.04; H, 6.83. Found : C, 73.80; H, 6.86.

Isosorbide derivatized alcohol 2-14. The Wittig adduct **2-13** (0.54 mmol, 0.35 g) was dissolved in acetonitrile (0.5 M) and cooled to 0°C. To this solution, 49% HF (0.54 mmol) was added by syringe. The reaction was monitored by TLC. Workup entailed an extraction with brine and chloroform. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 10:90), leaving a colorless, residual oil **2-14** (0.20 g, 90%).

2-14 : R_f= 0.13 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 2.48 (c = 2.5, chloroform); ^{1}H NMR ($CDCl_3$) 8.05 (d, 15.9 Hz, 1H), 7.55 (m, 4H), 7.2-7.4 (m, 15H), 6.32 (d, 15.8 Hz, 1H), 5.9 (d, 3.9 Hz, 1H), 4.68 (d, 11.9 Hz, 1H), 4.6 (d, 3.9 Hz, 1H), 4.55-4.4 (m, 4H), 4.5 (d, 12.0 Hz, 1H), 4.0 (d, 2.5 Hz, 1H), 3.8 (t, 6.4 Hz, 2H), 3.0 (t, 6.4 Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) 166.5, 142.8, 138.9, 137.1, 135.5, 135.4, 134.7, 133.5, 133.4, 131.1, 129.8, 129.5, 129.4, 128.5, 128.0, 127.7, 127.6, 127.57, 127.53, 126.7, 126.4, 119.0, 111.8, 105.2, 82.1, 81.5, 78.1, 71.8, 64.5, 62.2, 35.9, 26.8, 26.7, 26.5, 26.1, 19.0; IR (neat): 3054.3, 2937.8, 2856.2, 1711.5, 1635.7, 1216.2, 1012.3, 703.5, 616.1 cm^{-1}; HRMS calcd for $C_{24}H_{26}O_6$ 410.1729, found 410.1808.

Bromide 2-15. Alcohol **2-14** (0.85 mmol, 0.35 g) was dissolved in freshly distilled methylene chloride and cooled to 0°C. The reaction flask was purged with argon for

10 minutes. Triphenylphosphine (1.0 mmol, 0.27 g) was added and allowed to dissolve into solution. Carbon tetrabromide (0.94 mmol, 0.31 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 65:35), leaving a residual oil **2-15** (0.33 g, 82%).

2-15 : R_f= 0.53 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 111.7 (c = 0.12, chloroform); ^{1}H NMR ($CDCl_3$) 7.98 (d, 15.8 Hz, 1H), 7.6 (m, 1H), 7.4-7.2 (m, 7H), 6.4 (d, 15.6Hz, 1H), 5.33 (d, 3.5 Hz, 1H), 4.79 (d, 11.9 Hz, 1H), 4.7 (m, 1H), 4.55 (d, 11.7 Hz, 1H), 4.5 (m, 1H), 4.2-4.06 (m, 3H), 3.9 (dd, 8.8 Hz, 1H), 3.7 (dd, 8 Hz, 1H), 3.5 (t, 7.4 Hz, 2H), 3.3 (t, 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) 165.7, 142.3, 138.4, 137.6, 133.0, 130.6, 130.5. 129.1, 128.5, 128.0, 127.7, 127.0, 119.5, 86.0, 80.6, 79.1, 78.7, 73.8, 72.5, 70.4, 36.4, 32.1; IR (neat): 2953.8, 2877.6, 1714.1, 1626.9, 1169.2, 1054.8, 727.9 cm^{-1}; HRMS calcd for $C_{24}H_{25}O_5Br$ 472.1085, found 472.0964.

1,2:3,5-bis(*O*-Isopropylidene)-α-D-xylofuranose 2-17.[78] D-xylose **2-16** (68.2 mmol, 10.25 g) was dissolved in reagent grade acetone (200 mL). 2,2-Dimethoxypropane (50 mL) and *p*-toluenesulfonic acid (13.6 mmol, 2.5 g) were added to the mixture. The reaction was allowed to stir at room temperature for 24 hours or until all of the undissolved sugar went into solution. The reaction mixture was quenched with sodium bicarbonate until a neutral pH was achieved. The mixture was concentrated and the diacetonide was extracted with chloroform. A yellow, thick oil **2-17** was retrieved upon concentration of the chloroform washes (14.58 g, 92%).

2-17 : ^{1}H NMR ($CDCl_3$) 6.0 (d, 1H), 4.55 (d, 1H), 4.3 (m, 1H), 4.1 (m, 3H), 1.5 (s, 3H), 1.45 (s, 3H), 1.4 (s, 3H), 1.3 (s, 3H). All spectral data is in agreement with known literature values.[78]

1,2-*O*-Isopropylidene-α-D-xylofuranose 2-2.[79] 1,2:3,5-bis(*O*-Isopropylidene)-α-D-xylofuranose (**2-17**) (14.58 g, 63.4 mmol) was combined with a 70% solution of acetic acid (30 mL). The reaction was stirred for at least two days and monitored by TLC. The mixture was quenched with sodium bicarbonate and extracted with chloroform. The remaining acetic acid was removed by vacuum leaving a white solid **2-2** (m.p. 68-70°C) (8.23 g, 68.2 %).

2-2 : ^{1}H NMR ($CDCl_3$) 6.0 (d, 1H), 4.5 (d, 1H), 4.3 (m, 1H), 4.1 (m, 3H), 1.5 (s, 3H), 1.35 (s, 3H). All spectral data is in agreement with known literature values.[79]

Monoacetonide, monobenzylated xylose 2-6.[80] Sodium hydride (60% mass) (26.7 mmol, 1.07 g) was added to a flask flushed with argon. The gray powder was washed three times with pentane to remove the protective oil. Slowly, 1,2-O-isopropylidene-D-xylofuranose **2-2** (26.4 mmol, 5.03 g), diluted in DMF (30 mL), was added. The mixture was stirred for 20 minutes. Benzylbromide (26.7 mmol, 3.2 mL) was added to the reaction flask and allowed to stir for 15 hours at room temperature. Workup entailed an extraction with brine and diethyl ether. The organic layer was dried with anhydrous magnesium sulfate and concentrated. The product was isolated by flash chromatography with silica gel (hexane/ether 35:65), leaving a colorless, residual oil **2-6** (4.9 g, 66 %).

2-6 : R_f= 0.11 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 5.97 (d, 4 Hz, 1H), 4.60 (m, 2H), 4.50 (d, 4 Hz, 1H), 4.27 (m, 1H), 4.25 (dd, 7, 4 Hz, 1H), 3.93 (dd, 11, 4 Hz, 2H), 3.90 (dd, 11, 4 Hz, 2H), 3.68 (s, 1H), 1.48 (s, 3H), 1.31 (s, 1H). All spectral data is in agreement with known literature values.[80]

Chloro-esterified xylose 2-18.[52] The monobenzylated xylose **2-6** (14.3 mmol, 4.0 g) was dissolved in chloroform (80 mL). The solution was cooled to 0°C in an ice-bath and allowed to stir for 10 minutes. After addition of pyridine (57.1 mmol, 4.7 mL), the reaction was stirred at 0°C for 15 minutes. In a separate flask, chloroacetic anhydride (42.8 mmol, 7.3 g) was dissolved in chloroform (70 mL). This solution was added dropwise to the above reaction mixture. The reaction was stirred at room temperature for 12 hours. Workup entailed extraction with brine and chloroform. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 45:55), leaving a residual oil **2-18** (4.0 g, 78 %).

2-18 : R_f= 0.11 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = - 40.8 (c = 3.2, chloroform); ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H), 5.96 (d, 3.9 Hz, 4H), 4.7 (d, 12 Hz, 1H), 4.63 (d, 3.7 Hz, 1H), 4.4 (d, 12 Hz, 1H), 4.42-4.38 (m, 4H), 4.0 (s, 2H), 3.9 (d, 2.5 Hz, 1H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$) 166.9, 136.9, 128.4, 128.0, 127.7, 111.8, 105.2, 81.9, 81.3, 77.6, 71.7, 63.7, 40.6, 26.7, 26.1; IR (neat): 2989.1, 2936.5, 2254.3, 1759.8, 1454.9, 1375.4, 1015.8, 735.7, 700.1 cm^{-1}; HRMS calcd for $C_{17}H_{21}ClO_6$ 356.1027, found 356.1105; Anal. Calcd for $C_{17}H_{21}ClO_6$: C, 57.23; H, 5.93. Found: C, 56.95; H, 5.79.

Xylose Wittig reagent 2-19. Ester **2-18** (48.2 mmol, 17.2 g) was mixed with triphenylphosphine (144.0 mmol, 37.8 g) and benzene (96 mL) and allowed to reflux for 15 hours. The resulting solution was cooled to room temperature. Benzene (20 mL) was added to the mixture to solubilize the excess triphenylphosphine. This procedure was repeated 3 times, discarding the benzene layer. Hot water was added to dissolve the salt formed in the flask. Once dissolved, 0.1 M NaOH was added dropwise until no further white ppt was formed. More ppt. was observed upon cooling of the flask in an ice-bath for 1 hour. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was thoroughly dried by a vacuum pump to give **2-19** (23.7 g, 85 %).

2-19 : R_f= 0.054 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = - 8.9 (c = 5.7, chloroform); ^{1}H NMR ($CDCl_3$) of chloride salt 7.9-7.6 (m, 15H), 7.28 (m, 5H), 5.85 (d, 3.6 Hz, 1H), 4.6 (d, 12 Hz, 1H), 4.57 (d, 3.7 Hz, 1H), 4.4 (d, 12 Hz, 1H), 4.28 (m, 1H), 4.17 (m, 2H), 3.85 (d, 3.0 Hz, 1H), 3.3 (d, 13.5 Hz, 2H), 1.4 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$) 136.6, 134.8, 134.7, 133.6, 133.5, 132.9, 132.8, 130.2, 130.0, 129.9, 129.8, 128.2, 127.7, 127.4, 119.4, 111.5, 104.8, 81.5, 81.0, 71.4, 26.5, 25.8; IR (neat): 3354.1, 3060.3, 2990.5, 2712.2, 2173.7, 1736.5, 1710.5, 1588.0, 1439.0, 1374.4, 1115.2, 927.4, 737.8, 638.4 cm^{-1}; HRMS calcd for $C_{35}H_{35}O_6P$ 582.2171, found 582.2265.

Wittig adduct 2-20. TBDPS aldehyde **2-12** (2.6 mmol, 1.0 g) and Wittig reagent **2-19** (5.2 mmol, 3.0 g) were combined in a oven dried flask. The reaction was stirred

for 15 hours at room temperature. After completion, the remaining residue was subjected to column chromatography (hexane/ether 50:50) (1.0 g, 56 %).

2-20 : R_f= 0.73 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = - 20.4 (c = 1.7, chloroform); ^{1}H NMR ($CDCl_3$) 8.05 (d, 15.9 Hz, 1H), 7.55 (m, 4H), 7.2-7.4 (m, 15H), 6.32 (d, 15.8 Hz, 1H), 5.9 (d, 3.9 Hz, 1H), 4.68 (d, 11.9 Hz, 1H), 4.6 (d, 3.9 Hz, 1H), 4.55-4.4 (m, 4H), 4.5 (d, 12.0 Hz, 1H), 4.0 (d, 2.5 Hz, 1H), 3.8 (t, 6.4 Hz, 2H), 3.0 (t, 6.4 Hz, 2H), 1.49 (s, 3H), 1.32 (s, 3H), 0.98 (s, 9H); ^{13}C NMR ($CDCl_3$) 166.5, 142.8, 138.9, 137.1, 135.5, 135.4, 134.7, 133.5, 133.4, 131.1, 129.8, 129.5, 129.4, 128.5, 128.0, 127.7, 127.6, 127.57, 127.53, 126.7, 126.4, 119.0, 111.8, 105.2, 82.1, 81.5, 78.1, 71.8, 64.5, 62.2, 35.9, 26.8, 26.7, 26.5, 26.1, 19.0; IR (neat): 3054.3, 2937.8, 2856.2, 1711.5, 1635.7, 1216.2, 1012.3, 703.5, 616.1 cm^{-1}; HRMS calcd for $C_{42}H_{48}SiO_7$ 692.3169, found 692.3248; Anal. Calcd for $C_{42}H_{48}SiO_7$: C, 72.80; H, 6.98. Found : C, 72.65; H, 7.09.

Xylose derivatized alcohol 2-21. The Wittig adduct **2-20** (1.4 mmol, 1.0 g) was dissolved in pyridine (0.5 M) and cooled to 0°C. To this mixture, a commerical 65% hydrogen flouride/pyridine solution (1.5 mmol) was added by syringe. The reaction was monitored by TLC. Workup entailed an extraction with brine and chloroform. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 10:90), leaving a colorless, residual oil (0.55 g, 86 %).

2-21 : R_f= 0.19 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = - 28.6 (c = 2.5, chloroform); ^{1}H NMR ($CDCl_3$) 8.03 (d, 15.8 Hz, 1H), 7.58 (m, 1H), 7.4-7.23 (m, 8H), 6.4 (d, 15.8 Hz, 1H), 6.0 (d, 3.9 Hz, 1H), 4.72 (d, 11.9 Hz, 1H), 4.65 (d, 3.85 Hz, 1H), 4.55 (d, 11.9

Hz, 1H), 4.49-4.3 (m, 3H), 4.0 (d, 2.3 Hz, 1H), 3.8 (t, 6.75 Hz, 2H), 3.0 (t, 6.75 Hz, 2H), 1.5 (s, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$) 166.6, 142.5, 138.1, 137.1, 133.4, 130.8, 130.2, 128.5, 128.0, 127.7, 127.1, 126.8, 119.3, 111.9, 105.3, 82.1, 81.6, 78.2, 71.9, 63.3, 62.4, 36.4, 26.8, 26.2; IR (neat): 3474.2, 2939.0, 2869.1, 1713.2, 1631.7, 1596.6, 1375.7, 1166.3, 1079.0, 1012.3, 738.0, 699.4 cm^{-1}; HRMS calcd for $C_{26}H_{30}O_7$ for 454.1992, found 454.2070.

Bromide 2-22. Alcohol **2-21** (0.22 mmol, 0.10 g) was dissolved in distilled methylene chloride (0.44 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (0.26 mmol, 0.07 g) was added and allowed to dissolve into solution. Carbon tetrabromide (0.24 mmol, 0.08 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 65:35), leaving a residual oil **2-22** (0.10 g, 90 %).

2-22 : R_f= 0.65 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = - 26.9 (c = 2.1, chloroform); ^1H NMR ($CDCl_3$) 7.95 (d, 15.8 Hz, 1H), 7.58 (m, 1H), 7.4-7.2 (m, 8H), 6.4 (d, 15.8 Hz, 1H), 6.0 (d, 3.7 Hz, 1H), 4.71 (d, 11.9 Hz, 1H), 4.64 (d, 3.85 Hz, 1H), 4.5-4.4 (m, 5H), 4.0 (d, 2.3 Hz, 1H), 3.5 (t, 7.9, 7.3 Hz, 2H), 3.3 (t, 7.3, 7.7 Hz, 2H), 1.5 (s, 3H), 1.3 (s, 3H); ^{13}C NMR ($CDCl_3$) 166.4, 141.6, 138.2, 137.1, 133.1, 130.5, 130.2. 128.5, 128.0, 127.7, 127.6, 126.9, 119.9, 111.8, 105.3, 82.1, 81.6, 78.1, 71.9, 62.4, 36.4, 32.0, 26.8,

26.2; IR (neat): 2931.0, 1713.4, 1361.1, 1454.8, 1319.7, 1166.9, 1072.9, 1014.1, 767.3, 696.8 cm^{-1}; HMRS for $C_{24}H_{25}O_5Br$ calcd 516.1348, found 516.1221.

General Procedure for Radical Cyclizations. Bromide **2-15** (0.13 mmol, 0.06 g) and methylene chloride (0.5 M) were added to an argon flushed, oven-dried, round bottom flask. The Lewis acid (2 equiv.) was also added to the reaction vessel and allowed to stir under argon at room temperture for 15 minutes. The reaction mixture was then cooled to –78 °C with a dry ice/acetone bath. Tributyltin hydride (0.63 mmol, 0.17 mL) and triethylborane (1 M in hexane) (0.32 mmol, 0.32 mL) were then added to the solution in that order. After all the reagents were allowed to stir at –78 °C for ten minutes, oxygen was bubbled into the mixture for five minute intervals every three hours. The reaction was monitored by TLC until completion. Workup entailed concentrating the mixture and applying it to a pad of potassium flouride on top of a column of silica gel. After leaving the residue on the pad for thirty minutes, the cyclized product was eluted (30:60 ether:hexane) yielding **2-23** (0.43 g, 84 %). **2-23** : R_f= 0.50 (35:65 EtOAc:Hex); ^1H NMR ($CDCl_3$) 7.35 (m, 5H), 7.16 (m, 4H), 5.23 (d, 3.7 Hz, 1H), 4.75 (d, 12 Hz, 1H), 4.65 (t, 4.4 Hz, 1H), 4.55 (d, 12 Hz, 1H), 4.46 (t, 5 Hz, 1H), 4.06 (m, 3H), 3.9 (t, 8.9 Hz, 1H), 3.65 (t, 8.3 Hz, 1H), 3.57 (m, 1H), 2.8 (m, 3H), 2.42 (m, 2H), 1.75 (m, 1H); ^{13}C NMR($CDCl_3$) 171.5, 143.0, 135.1, 128.5, 127.9, 126.8, 126.3, 124.6, 123.4, 85.9, 80.6, 79.1, 78.5, 73.8, 72.5, 70.4, 41.2, 39.7, 32.2, 31.2; IR (neat): 2927.7, 2847.8, 2358.6, 1735.0, 1660.2, 1635.2, 1455.5, 1365.6, 1255.8, 1161.0, 1101.1, 1056.1, 986.3, 746.6, 691.7 cm^{-1}; HRMS calcd for $C_{25}H_{26}O_5$ 394.1780, found 394.2185.

2-24 : R_f= 0.59 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 7.31 (m, 5H), 7.15 (m, 4H), 5.96 (d, 3.7 Hz, 1H), 4.70 (d, 11.9 Hz, 1H), 4.60 (d, 3.67 Hz, 1H), 4.5-4.3 (m, 4H), 3.95 (d, 1.9 Hz, 1H), 3.57 (t, 6.7, 7.5 Hz, 1H), 2.8 (m, 3H), 2.4 (m, 2H), 1.7 (m, 1H), 1.49 (s, 3H), 1.32 (s, 3H); ^{13}C NMR($CDCl_3$) 172.5, 143.8, 137.2, 128.5, 128.1, 127.7, 126.7, 126.3, 124.5, 123.4, 111.8, 105.3, 82.1, 81.6, 78.1, 71.9, 62.2, 41.2, 39.7, 32.3, 31.2, 26.8, 26.3; IR (neat): 2957.6, 2917.7, 2348.6, 1730.0, 1455.5, 1370.6, 1260.8, 1210.9, 1161.0, 1071.1, 1011.2, 856.5, 746.6, 691.7 cm^{-1}; HRMS calcd for $C_{26}H_{30}O_6$ 438.2042, found 438.2036.

Indan acid 2-25.[48] Indanate ester **2-24** (0.14 mmol, 0.06 g) was dissolved in a 5:1 THF:H_2O solution and stirred at room temperature. To this flask, 10 equiv. of LiOH was added. The resulting reaction mixture was heated at reflux for three hours. Reaction progress was monitored by TLC. The reaction mixture was first washed with ether to remove any organic contaminants, followed by neutralization of the basic solution with 2M HCl. An ethyl acetate wash removed the reprotonated alcohol product. Further acidification to pH 2 provided acid **2-25** (0.01 g, 42 %).
2-25 : R_f= 0.53 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ (isosorbide) = + 5.5 (c = 0.5, benzene); $[\alpha]^{25}_D$ (xylose) = + 3.5 (c = 0.9, benzene); ^{1}H NMR ($CDCl_3$) 7.25-7.1 (m, 4H), 3.58 (q, 7.5 Hz, 1H), 2.87 (m, 2H), 2.47 (m, 2H), 1.76 (m, 1H); ^{13}C NMR($CDCl_3$) 178.5, 145.7, 144.1, 126.9, 126.5, 124.8, 123.6, 41.2, 39.8, 32.5, 31.3; IR (neat): 2943.5, 2849.5, 2673.2, 1707.9, 1408.2, 1267.2, 1190.8, 750.1 cm^{-1}; HRMS calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0840.

4-Aza-tricyclo [5.2.1.0^{2,6}] dec-8-ene-3, 5-dione 3-4.[81] Commercially available malimide **3-3** (103 mmol, 10.0 g) was combined with freshly distilled cyclopentadiene (309 mmol, 20.4 g) in benzene (200 mL). The reaction mixture was refluxed overnight (12 hr.). Upon cooling, a white, crystalline precipitate formed. The crystals were filtered and washed with excess benzene to yield the Diels Alder adduct **3-4** (m.p. 187 °C, diethyl ether:ethanol) (15.8 g, 94.6 %).

3-4 : ^{1}H NMR ($CDCl_3$) 7.7 (br s, 1H), 6.20 (s, 2H), 3.39 (m, 2H), 3.31 (m, 2H), 1.77 (d, 8.9 Hz, 1H), 1.62 (s, 1H), 1.54 (d, 8.9 Hz, 1H). All spectral data is in agreement with known literature values.[81]

N-(4-Bromobutyl) bicyclo [2.2.1] hept-5-ene-2,3-di-exo-carboximide 3-5.[82] 4-aza-tricyclo[5.2.1.0^{2,6}] dec-8-ene-3,5-dione **3-4** (97 mmol, 15.8 g) was dissolved in reagent grade acetone (200 mL). To this solution was added potassium carbonate (194 mmol, 26.8 g) and 1,4 dibromobutane (194 mmol, 41.8 g). The mixture was allowed to stir overnight at room temperature. The resulting solution was concentrated and purified on a column of silica gel (hexane/ether 55:45), isolating a yellow oil **3-5** (24.5 g, 85 %).

3-5 : ^{1}H NMR ($CDCl_3$) 7.75 (br s, 1H), 6.20 (s, 2H), 3.39 (m, 2H), 3.31 (m, 2H), 1.77 (d, 8.9 Hz, 1H), 1.62 (s, 1H), 1.54 (d, 8.9 Hz, 1H). All spectral data is in agreement with known literature values.[82]

N-(Butyl-isosorbide) bicyclo [2.2.1] hept-5-ene-2,3-di-exo-carboximide 3-7. Sodium hydride (60% mass) (201 mmol, 0.8 g) was added to a flask flushed with

argon. The gray powder was washed three times with pentane to remove the protective oil. Slowly, isosorbide (20.1 mmol, 2.9 g), diluted in THF (20 mL), was added. The mixture was stirred for 20 minutes. The bromo succimide **3-5** (10.0 mmol, 3.0 g) and tetrabutylammoniuym bromide (10.0 mmol, 3.2 g), a phase transfer catalyst, were added to the reaction flask and allowed to stir for 15 hours at room temperature. Workup entailed concentration of the reaction mixture and an extraction with brine and ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and concentrated. The product was isolated by flash chromatography with silica gel (0:100 hexane:ethyl acetate), leaving a colorless, residual oil **3-7** (2.75 g, 76 %).

3-7 : R_f= 0.05 (35:65 EtOAc:Hex); $[\alpha]^{25}_D = +21.6$ (c = 7.3, chloroform); ^{1}H NMR ($CDCl_3$) 6.08 (s, 2H), 4.61 (m, 2H), 4.38 (m, 2H), 4.26 (m, 3H), 4.11 (m, 1H), 3.87 (m, 8H), 3.43 (m, 12H), 1.74 (m, 1H), 1.52 (m, 5H) ^{13}C NMR ($CDCl_3$) 177.52, 133.89, 87.81, 87.51, 85.16, 83.51, 81.18, 81.03, 79.71, 79.61, 79.47, 75.76, 75.70, 75.23, 75.15, 72.77, 72.23, 71.82, 71.75, 69.46, 69.30, 51.67, 51.67, 45.13, 44.31, 37.45, 26.43**;** IR (neat): 3401.1, 2942.7, 2872.2, 1766.2, 1689.8, 1625.2, 1401.9, 1366.7, 1337.3, 1078.7, 1008.2, 973.0, 884.8, 843.7, 773.2, 726.2, 608.7 cm^{-1}; HRMS calcd for $C_{19}H_{25}NO_6$ 363.1682, found 363.1760.

2-(3-Hydroxy-propyl)-benzyl alcohol 3-9.[83] 1,2-Dihydronapthalene **3-8** (190 mmol, 24.8 g) was dissolved in a methylene chloride:methanol (1:1) solution (380 mL). The mixture was cooled to -78°C with a dry ice/acetone bath. A constant stream of ozone was bubbled through the solution until a sky blue color was achieved. After the

excess ozone was quenched with oxygen, sodium borohydride (952 mmol, 36.1 g) was added at -78°C. The reaction was monitored by TLC. After the oxidation was complete, the mixture was concentrated and extracted with methylene chloride. No further purification of the diol **3-9** was necessary (22.7 g, 79 %).

3-9 : ^{1}H NMR ($CDCl_3$) 7.25 (m, 4H), 4.6 (s, 2H), 3.5 (t, 2H), 2.75 (t, 2H), 1.85 (m, 2H). All spectral data is in agreement with known literature values.[83]

2-(3-Hydroxy-propyl)-benzyl aldehyde 3-10.[84] Diol **3-9** (6.6 mmol, 1.0 g) was dissolved in freshly distilled benzene (15 mL). Activated manganese dioxide (5.0 g) was added to the mixture. The solution was stirred for 20 hr., or until all of the benzylic alcohol was oxidized. The excess manganese dioxide was filtered through Celite and the filtrate was concentrated. No further purification was necessary to give **3-10** (0.88 g, 88 %).

(3-10) : ^{1}H NMR ($CDCl_3$) 10.15 (s, 1H), 7.7 (d, 1H), 7.4 (m, 1H), 7.25 (m, 2H), 3.6 (m, 2H), 3.35 (br s, 1H), 3.05 (t, 2H), 1.8 (m, 2H). All spectral data is in agreement with known literature values.[84]

3-[2-(3-Hydroxy-propyl)-phenyl]-acrylic acid ethyl ester 3-11.[85] Aldehyde **3-10** (113 mmol, 17.0 g) was dissolved in methylene chloride (113 mL). Commercially available (carbethoxymethylene) triphenylphosphorane (147 mmol, 51.0 g) was added to the solution. The mixture was stirred overnight. As the reaction proceeded, the solution turned a light green color. After completion, the mixture was

concentrated and purified by flash chromatography (60:40 hexane:ether) to give **3-11** (17.8 g, 67 %).

3-11 : ^{1}H NMR ($CDCl_3$) 8.1 (d, 15.8 Hz, 1H), 7.62 (m, 1H), 7.27 (m, 3H), 6.37 (d, 15.8 Hz, 1H), 4.25 (m, 2H), 3.65 (m, 2H), 3.47 (m, 1H), 2.85 (t, 7.5 Hz, 2H), 1.85 (m, 2H), 1.35 (t, 3H). All spectral data is in agreement with known literature values.[85]

3-[2-(3-Bromo-propyl)-phenyl]-acrylic acid ethyl ester 3-29. Ethyl ester **3-11** (4.5 mmol, 1.0 g) was dissolved in distilled methylene chloride (9.0 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (5.5 mmol, 1.43 g) was added and allowed to dissolve into solution. Carbon tetrabromide (5.0 mmol, 1.67 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (85:15, hexane:ether), leaving a residual oil **3-29** (0.9 g, 67 %).

3-29 : R_f = 0.75 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 8.1 (d, 15.8 Hz, 1H), 7.62 (m, 1H), 7.27 (m, 3H), 6.37 (d, 15.6 Hz, 1H), 3.4 (t, 6.5 Hz, 2H), 2.95 (t, 7.5 Hz, 2H), 2.13 (q, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) 172.13, 144.04, 140.46, 132.63, 130.62, 130.35, 127.01, 118.89, 34.09, 32.73, 31.34; IR (neat): 2930.3, 2848.5, 1677.9, 1616.5, 1463.2, 1377.3, 1328.2, 1298.6, 1225.3, 956.4 cm^{-1}; HRMS calcd for $C_{12}H_{13}BrO_2$ 268.0299, found 268.0177.

3-[2-(3-Hydroxy-propyl)-phenyl]-acrylic acid (3-12). Ethyl ester **3-11** (36.4 mmol, 8.0 g) was dissolved in a 5:1 THF:H_2O solution and stirred at room temperature. To this flask, 10 equiv. of LiOH was added. The resulting reaction mixture was heated at reflux for three hours. Reaction progress was monitored by TLC. The reaction mixture was first washed with ether to remove any organic contaminants, followed by neutralization of the basic solution with 2 M HCl. An ethyl acetate wash removed the reprotonated alcohol product. Further acidification to pH 2 provided acid **3-12** (5.10 g, 68 %).

3-12 : R_f= 0.32 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 8.16 (d, 15.8 Hz, 1H), 7.61 (m, 1H), 7.31 (m, 3H), 6.42 (d, 15.8 Hz, 1H), 3.70 (t, 6.1 Hz, 2H), 2.89 (t, 7.7 Hz, 2H), 1.86 (m, 2H), 1.55 (br s, 1H). ^{13}C NMR ($CDCl_3$) 166.97, 141.91, 132.49, 129.8, 129.30, 128.28, 126.55, 125.17, 118.91, 61.27, 29.14, 13.94; IR (neat): 2950.7, 2684.9, 2572.4, 1713.7, 1688.1, 1626.8, 1422.3, 1366.3, 1243.2, 1096.8, 1032.0, 981.4, 878.0, 767.7 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.1021.

3-[2-(3-Bromo-propyl)-phenyl]-acrylic acid (3-13). Alcohol **3-12** (1.04 mmol, 0.20 g) was dissolved in distilled methylene chloride (2.0 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (1.25 mmol, 0.33 g) was added and allowed to dissolve into solution. Carbon tetrabromide (1.15 mmol, 0.38 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The

product was isolated by flash chromatography on silica gel (50:50, hexane:ether), leaving a residual oil **3-13** (0.18 g, 64 %).

3-13 : R_f= 0.55 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 8.1 (d, 15.8 Hz, 1H), 7.62 (m, 1H), 7.27 (m, 3H), 6.37 (d, 15.6 Hz, 1H), 3.4 (t, 6.5 Hz, 2H), 2.95 (t, 7.5 Hz, 2H), 2.13 (q, 6.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) 172.13, 144.04, 140.46, 132.63, 130.62, 130.35, 127.01, 118.89, 34.09, 32.73, 31.34; IR (neat): 2930.3, 2848.5, 1677.9, 1616.5, 1463.2, 1377.3, 1328.2, 1298.6, 1225.3, 956.4 cm^{-1}; HRMS calcd for $C_{12}H_{13}BrO_2$ 268.0299, found 268.0177.

2-Hydroxymethyl-phenethyl alcohol 3-15.[86] Indene **3-14** (172.2 mmol, 20.0 g) was dissolved in a methylene chloride:methanol (1:1) solution (344 mL). The mixture was cooled to -78°C with a dry ice/acetone bath. The initial recation color was red/orange. A constant stream of ozone was bubbled through the solution. The reaction underwent several color changes, going from red/orange to green. After the excess ozone was quenched with oxygen, sodium borohydride (860.9 mmol, 32.6 g) was added at -78°C, changing the reaction color to a pale yellow. The reaction was monitored by TLC. After the oxidation was complete, the mixture was concentrated and extracted with methylene chloride. No further purification of the diol **3-15** was necessary (21.4 g, 88 %).

3-15 : ^{1}H NMR ($CDCl_3$) 7.25 (m, 4H), 4.56 (s, 2H), 3.79 (t, 2H), 3.35 (br s, 2H), 2.88 (t, 2H). All spectral data is in agreement with known literature values.[86]

2-(2-Hydroxy-ethyl)-benzaldehyde (3-16).[87] Diol **3-15** (92.9 mmol, 13.0 g) was dissolved in freshly distilled benzene (200 mL). Activated manganese dioxide (65.0 g) was added to the mixture. The solution was stirred for 20 hr., or until all of the benzylic alcohol was oxidized. The excess manganese dioxide was filtered through Celite and the filtrate was concentrated. No further purification of **3-16** was necessary (11.0 g, 79 %).

3-16 : ^{1}H NMR ($CDCl_3$) 10.15 (s, 1H), 7.7 (d, 1H), 7.4 (m, 1H), 7.25 (m, 2H), 3.6 (m, 2H), 3.35 (br s, 1H), 3.05 (t, 2H). All spectral data is in agreement with known literature values.[87]

3-[2-(2-Hydroxy-ethyl)-phenyl]-acrylic acid ethyl ester 3-17. Aldehyde **3-16** (33 mmol, 5.0 g) was dissolved in methylene chloride (33 mL). Commercially available (carbethoxymethylene) triphenylphosphorane (43 mmol, 15.1 g) was added to the solution. The mixture was stirred overnight. As the reaction proceeded, the solution turned a light green color. After completion, the mixture was concentrated and purified by flash chromatography (25:75 hexane:ether) (6.1 g, 85 %).

3-17 : R_f = 0.54 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 7.9 (d, 15.9 Hz, 1H), 7.45 (m, 1H), 7.14 (m, 3H), 6.27 (d, 15.8 Hz, 1H), 4.13 (m, 2H), 3.68 (m, 2H), 3.45 (m, 1H), 2.90 (m, 2H), 1.21 (t, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) 166.66, 141.62, 138.05, 133.23, 130.31, 129.61, 126.84, 126.06, 119.0, 66.88, 62.62, 60.08, 35.96; IR (neat): 3426.3, 2949.9, 2870.6, 1701.0, 1631.5, 1596.8, 1482.6, 1447.9, 1363.6, 1314.0, 1274.3, 1180.0, 981.5, 862.4, 763.2, 728.5 cm^{-1}; HRMS calcd for $C_{13}H_{16}O_3$ 220.1099,

found 220.1177 ; Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found : C, 70.52; H, 7.41.

3-[2-(2-Bromo-ethyl)-phenyl]-acrylic acid ethyl ester 3-30. Ethyl ester **3-17** (7.3 mmol, 1.6 g) was dissolved in distilled methylene chloride (15.0 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (8.8 mmol, 2.3 g) was added and allowed to dissolve into solution. Carbon tetrabromide (8.1 mmol, 2.68 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (80:20, hexane:ether), leaving a residual oil **3-30** (1.5 g, 73 %). **(3-30)** : R_f= 0.80 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 7.95 (d, 15.8 Hz, 1H), 7.55 (m, 1H), 7.29 (m, 3H), 6.37 (d, 15.8 Hz, 1H), 4.28 (q, 7.1 Hz, 2H), 3.50 (t, 7.5 Hz, 2H), 3.30 (t, 7.5 Hz, 2H), 1.34 (t, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) 166.56, 140.96, 138.06, 133.20, 130.41, 130.02, 127.52, 126.83, 120.53, 60.50, 36.36, 31.98, 14.22; IR (neat): 2979.9, 1711.7, 1634.0, 1484.2, 1448.9, 1307.9, 1260.9, 1172.8, 1031.7, 978.8, 861.3, 761.4 cm^{-1}; HRMS calcd for $C_{13}H_{15}BrO_2$ 282.0455, found 282.0334.

3-[2-(2-*t*-Butyl dimethyl silyl ether-ethyl)-phenyl]-acrylic acid ethyl ester 3-18. Ethyl ester **3-17** (2.7 mmol, 0.6 g) was dissolved in dimethyl formamide (6 mL). Imidazole (0.74 g, 10.9 mmol) and DMAP (0.066 g, 0.54 mmol) were added to the recation mixture. The resulting solution was purged of oxygen and moisture with

argon. *t*-Butyl dimethylsilyl chloride (0.74 g, 1.8 mmol) was added to the flask and the reaction was allowed to stir overnight. The product was extracted with ether, dried and subjected to flash chromatography (95 :5 hexane :ether), isolating a light yellow oil **3-18** (0.81 g, 88%).

3-18 : R_f= 0.91 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 8.11 (d, 15.8 Hz, 1H), 7.59 (m, 1H), 7.27 (m, 3H), 6.42 (d, 15.8 Hz, 1H), 4.32 (q, 7.1 Hz, 2H), 3.81 (t, 6.9 Hz, 2H), 3.01 (t, 6.9 Hz, 2H), 1.38 (t, 7.1 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) 166.73, 142.14, 138.65, 133.55, 130.93, 129.72, 126.71, 126.33, 119.61, 63.96, 60.30, 36.55, 25.78, 18.15, 14.24, -5.62; IR (neat): 2931.6, 2861.0, 1714.8, 1634.1, 1467.8, 1367.0, 1311.5, 1256.5, 1170.4, 1094.8, 1034.3, 978.8, 913.3, 832.6, 772.2 cm^{-1}; HRMS calcd for $C_{19}H_{30}O_3Si$ 334.1964, found 334.2042 ; Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found : C, 68.20; H, 9.41.

Succinimide ester 3-21. Carboxylic acid **3-13** (3.7 mmol, 1.0 g) was combined in an oven-dried flask with 1,3-dicyclohexylcarbodiimide (DCC) (11.15 mmol, 2.3 g) and 4-dimethyl-aminopyridine (DMAP) (1.2 mmol, 0.14 g) in methylene chloride (7.4 mL). The mixture was stirred at ambient temperature for 1 hour. To this solution was added the succimide ether **3-7** (11.1 mmol, 4.0 g). The mixture was stirred overnight. The reaction was concentrated and the ester product **3-21** was purified by flash chromatography (0:100 hexane:ether) to give **3-21** (mp 220°C), (2.0 g, 86 %).

3-21 : R_f= 0.22 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = +36.34 (c = 0.71, chloroform); ^{1}H NMR ($CDCl_3$) 8.05 (d, 15.8 Hz, 1H), 7.57 (m, 1H), 7.27 (m, 3H), 6.39 (d, 15.8 Hz, 1H), 6.09 (s, 2H), 5.31 (d, 3.0 Hz, 1H), 4.71 (t, 4.4 Hz, 1H), 4.60 (d, 4.4 Hz, 1H),

4.02 (m, 4H), 3.66 (m, 1H), 3.40 (m, 6H), 2.9 (t, 7.5 Hz, 2H), 2.11 (t, 7.5 Hz, 2H), 1.95 (m, 1H), 1.62 (m, 6H), 1.35 (m, 2H), 1.11 (m, 2H), 0.92 (t, 7.3 Hz, 1H) ; ^{13}C NMR ($CDCl_3$) 177.68, 165.79, 142.75, 140.34, 134.41, 132.76, 130.39, 130.29, 126.94, 126.78, 118.94, 86.06, 80.54, 80.23, 78.67, 73.74, 70.34, 69.98, 52.18, 49.09, 45.69, 44.87, 37.96, 34.10, 33.93, 32.86, 31.32, 27.03, 25.59, 24.91, 24.43; IR (neat): 3322.1, 2928.8, 2848.7, 1689.8, 1625.2, 1401.9, 1166.9, 1090.5, 1049.4, 767.3, 726.2 cm^{-1}; HRMS calcd for $C_{31}H_{36}BrNO_7$ 613.1875, found 613.1723.

ROMP polymer 3-22. Succinimide ester **3-21** (0.16 mmol, 0.10 g) was dissloved in freshly distilled methylene chloride. The reaction vessel was purged with argon for 20 minutes. A catalytic amount of Grubb's catalyst, bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride, (0.005 mmol, 0.004 g) was added to the mixture. The initial color of the reaction was a deep purple. This eventually changed over the course of two days to a dark green. The polymerization was allowed to proceed for another day until a capping agent, (ethyl-vinyl ether 2.0 mL) was added. The resulting mixture stirred for 2 more hours, at which point the solution was concentrated and slowly added to room temperature methanol. A dark brown precipitate **3-22** was formed, filtered, washed with excess methanol, and dried to give **3-22** (0.09 g, 90 %).

3-22 : ^{1}H NMR ($CDCl_3$) 8.02 (d, 1H), 7.57 (d, 1H), 7.32 (m, 3H), 6.40 (d, 16.0 Hz, 1H), 5.68 (s, 1H), 5.30 (s, 1H), 4.69 (m, 1H), 4.59 (m, 1H), 3.99 (m, 5H), 3.69-3.19 (m, 11H), 2.92 (m, 3H), 2.11-1.25 (m, 11H); ^{13}C NMR ($CDCl_3$) 206.88, 177.66, 165.76, 142.72, 140.33, 134.38, 132.72, 130.37, 130.27, 126.92, 126.75, 118.91,

86.03, 80.52, 80.20, 78.64, 74.18, 73.70, 73.20, 70.31, 69.95, 52.15, 49.04, 45.66, 44.83, 37.91, 34.08, 33.87, 32.83, 31.28, 30.86, 29.62, 26.99, 25.56, 24.88, 24.39. Mn = 8287, PDI = 1.300.

General procedure for radical cyclizations on polymer support. Polymer supported succimide ester **3-22** or **3-24** (0.006 mmol, 0.04 g) and methylene chloride (0.012 mL) were added to an argon flushed, oven-dried, round bottom flask. The Lewis acid (2 equiv.) was also added to the reaction vessel and allowed to stir under argon at room temperture for 15 minutes. The reaction mixture was then cooled to -78 °C with a dry ice/acetone bath. Tributyltin hydride (0.085 mL, 0.032 mmol) and triethylborane (1M in hexane) (0.06 mL, 0.06 mmol) were then added to the solution in that order. After all the reagents were allowed to stir at -78 °C for ten minutes, oxygen was bubbled into the mixture for five minute intervals every three hours. Since product formation could not be monitored by TLC, the reaction was continued for 10 h. To ensure completion. Workup entailed concentrating the mixture and subjecting **3-25** or **3-26** to saponification conditions (0.04 g).

(1,2,3,4-Tetrahydro-naphthalen-1-yl)-acetic acid 3-27.[88] The polymer-supported cyclized adduct **3-25** (0.073 mmol, 0.04 g) was dissolved in a 5:1 THF:H_2O solution and stirred at room temperature. To this flask, 10 equiv. of LiOH was added. The resulting reaction mixture was heated at reflux for three hours. Reaction progress was monitored by TLC. The reaction mixture was first washed with ether to remove any organic contaminants, followed by neutralization of the basic solution with 2M HCl.

An ethyl acetate wash removed the reprotonated alcohol product. Further acidification to pH 2 provided acid **3-27** (0.01 g, 72 %).

3-27 : R_f= 0.69 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 10.72 (br s, 1H), 7.11 (m, 4H), 3.35 (t, 5.0 Hz, 1H), 2.76 (m, 3H), 2.58 (m, 1H), 1.81 (m, 4H); ^{13}C NMR($CDCl_3$) 179.34, 138.89, 137.12, 129.29, 128.16, 126.10, 125.87, 41.75, 34.30, 29.44, 28.03, 19.44; IR (neat): 2934.3, 2861.9, 1701.6, 1489.5, 1448.1, 1406.7, 1292.9, 1204.9, 946.3, 910.1, 760.1 cm^{-1}; HRMS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.1075.

Mono TBS alcohol 4-9.[89] Sodium hydride (322 mmol, 12.9 g) was suspended in THF (644 mL) after being washed with pentane. Ethylene glycol (322 mmol, 20.0 g) was added to the mixture at room temperature and stirred for 20 minutes. *Tert*-butyldimethylsilyl chloride was then added and vigorous stirring was continued for a hour. The mixture was poured into ether, washed with 10% aqueous potassium carbonate and brine, dried with sodium sulfate and concentrated. The resulting oil was purified by flash chromatography (hexane/ethyl acetate 70:30), leaving a colorless, residual oil **4-9** (31.9 g, 56 %).

4-9 : R_f= 0.19 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 3.62 (m, 2H), 3.55 (m, 2H), 2.80 (br s, 1H), 0.82 (s, 9H), 0.06 (s, 6H). All spectral data is in agreement with known literature values.[89]

Allyl ether 4-10. Sodium hydride (60% mass) (25 mmol, 1.0 g) was added to a flask flushed with argon. The gray powder was washed three times with pentane to remove the protective oil. A dilute solution of the TBS alcohol **4-9** (22.7 mmol, 4.0 g) in

THF (44 mL) was added to the reaction flask. The mixture was stirred for 20 minutes. Allyl bromide (29.5 mmol, 2.6 mL) was added to the reaction flask and allowed to stir for 4 hours at ambient temperature. The reaction was monitored by TLC. Workup entailed concentration of the reaction mixture, and an extraction with brine and diethyl ether. The organic layer was dried with anhydrous magnesium sulfate and the solution concentrated. The product was isolated by flash chromatography with silica gel (hexane/ether 85:15), leaving a colorless, residual oil **4-10** (4.5 g, 92%).

4-10 : R_f= 0.62 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 5.89 (m, 1H), 5.24 (dd, 2H), 4.02 (d, 5.6 Hz, 2H), 3.77 (t, 5.4 Hz, 2H), 3.52 (t, 5.0 Hz, 2H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$) 134.92, 116.68, 72.20, 71.60, 62.75, 25.93, 18.38, -5.28; IR (neat): 2928.0, 1463.3, 1355.9, 1253.7, 1141.2, 1105.5, 1003.2, 936.8, 829.4, 773.2 cm^{-1}; HRMS calcd for $C_{11}H_{24}O_2$ 216.1546, found 216.1623.

Aldehyde ether 4-11. Allyl ether **4-10** (9.3 mmol, 2.0 g) was dissolved in freshly distilled methylene chloride (10 mL) and cooled to -78 °C. A steady stream of ozone was bubbled into the solution until a sky blue color was achieved. The remaining ozone was quenched with excess oxygen. Dimethyl sulfide (18.5 mmol, 1.15 g) was added to the reaction mixture at -78 °C and the resulting solution was allowed to warm to room temperature. The mixture was stirred overnight. The product mixture was washed with water and concentrated, yielding the product aldehyde **4-11** (1.9 g, 93.2 %).

4-11 : R_f= 0.88 (35:65 EtOAc:Hex) ^{1}H NMR ($CDCl_3$) 9.66 (s, 1H), 4.09 (s, 1H), 3.75 (t, 4.9 Hz, 2H), 3.58 (t, 4.4 Hz, 2H), 0.84 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$) 200.94, 76.81, 73.24, 62.79, 25.74, 18.17, -5.49; IR (neat): 2931.0, 2860.5, 1725.1, 1437.2, 1260.9, 1119.9, 1031.7, 837.8, 720.3, 690.9 cm^{-1}; HRMS calcd for $C_{10}H_{22}SiO_3$ 218.1338, found 218.1416.

(+)-Isosorbide Wittig reagent 4-7. See experimental for compound **2-10**.

(+)-Isosorbide ester 4-12. Aldehyde ether **4-11** (2.3 mmol, 0.5 g) was dissolved in freshly distilled methylene chloride (2.3 mL). To this solution was added the (+)-isosorbide Wittig reagent **4-7** (1.5 mmol, 0.8 g). The reaction stirred overnight. The mixture was concentrated and purified by flash chromatography providing a thick oil **4-12** (0.8 g, 73 %).

4-12 : R_f= 0.89 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 75.2 (c = 4.1, chloroform); ^{1}H NMR ($CDCl_3$) 7.34 (m, 5H), 6.47 (m, 1H), 5.81 (m, 1H), 5.20 (d, 3.7 Hz, 1H), 4.74 (d, 11.75 Hz, 1H), 4.68 (t, 4.6 Hz, 1H), 4.56 (m, 5H), 4.06 (m, 3H), 3.88 (m, 1H), 3.77 (t, 5.2 Hz, 2H), 3.66 (m, 1H), 3.54 (t, 5.2 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) 164.71, 150.35, 137.56, 128.39, 127.84, 118.31, 85.89, 80.53, 78.98, 78.35, 73.61, 72.41, 72.25, 70.30, 69.21, 62.51, 25.85, 18.29, -5.32; IR (neat): 2934.3, 2861.9, 1722.2, 1660.2, 1453.2, 1360.1, 1303.2, 1272.2, 1168.7, 1106.7, 1049.8, 1013.5, 961.8, 785.9, 734.2, 698.0 cm^{-1}; HRMS calcd for $C_{25}H_{38}O_7Si$ 478.2387, found 478.2465.

Isosorbide derivatized alcohol 4-13. The Wittig adduct **4-12** (0.012 mmol, 0.06 g) was dissolved in acetonitrile (0.5 M) and cooled to 0°C. To this solution, 49% HF (0.014 mmol) was added by syringe. The reaction was monitored by TLC. Workup entailed an extraction with brine and chloroform. The organic layer was dried with anhydrous magnesium sulfate and the solution was concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 10:90), leaving a colorless, residual oil **4-13** (0.03 g, 66 %).

4-13 : R_f = 0.11 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 79.3 (c = 2.3, chloroform); ^{1}H NMR ($CDCl_3$) 7.34 (m, 5H), 6.44 (m, 1H), 5.83 (m, 1H), 5.20 (d, 3.7 Hz, 1H), 4.74 (d, 11.75 Hz, 1H), 4.68 (t, 4.6 Hz, 1H), 4.56 (m, 5H), 4.14-3.56 (m, 9H), 2.43 (br s, 1H); ^{13}C NMR ($CDCl_3$) 164.68, 149.38, 137.48, 128.36, 127.80, 127.55, 118.75, 85.81, 80.50, 78.90, 78.36, 73.52, 72.38, 71.82, 70.27, 68.89, 61.52; IR (neat): 3471.6, 2942.7, 2872.2, 1725.1, 1654.6, 1490.1, 1448.9, 1360.8, 1266.8, 1178.6, 890.7, 837.8, 743.8, 696.8 cm^{-1}; HRMS calcd for $C_{19}H_{24}O_7$ 364.1522, found 364.1600.

Bromide 4-14. Alcohol **4-13** (0.082 mmol, 0.03 g) was dissolved in distilled methylene chloride (0.16 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (0.099 mmol, 0.026 g) was added and allowed to dissolve into solution. Carbon tetrabromide (0.091 mmol, 0.03 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried with anhydrous magnesium sulfate and concentrated. The product was isolated by flash

chromatography on silica gel (hexane/ether 65:35), leaving a residual oil **4-7** (0.25 g, 71%).

4-14 : R_f= 0.82 (35:65 EtOAc:Hex); $[\alpha]^{25}_D$ = + 46.1 (c = 2.5, chloroform); ^{1}H NMR ($CDCl_3$) 7.30 (m, 5H), 6.97 (m, 1H), 6.14 (m, 1H), 5.24 (m, 1H), 4.75 (d, 11.9 Hz, 1H), 4.70 (m, 1H), 4.57 (m, 2H), 4.23-3.99 (m, 5H), 3.91-3.56 (m, 6H), 3.47 (m, 1H); ^{13}C NMR ($CDCl_3$) 164.95, 144.82, 137.55, 135.32, 128.36, 127.80, 127.55, 120.63, 85.81, 80.50, 78.90, 78.36, 73.52, 72.38, 71.82, 70.27, 69.45, 29.99; IR (neat): 2931.0, 2860.5, 1725.1, 1660.5, 1454.8, 1354.9, 1302.0, 1272.6, 1166.9, 1102.2, 1014.1, 790.8, 743.8, 696.8 cm^{-1}; HRMS calcd for $C_{19}H_{23}O_6Br$ 426.0878, found 426.0756.

Racemate bromide 4-17. Aldehyde **4-11** (4.6 mmol, 1.0 g) was dissolved in freshly distilled methylene chloride (4.6 mL). Commercially available (carbethoxymethylene) triphenylphosphorane (5.96 mmol, 2.08 g) was added to the solution. The mixture was stirred overnight. As the reaction proceeded, the solution turned a light yellow color. After completion, the mixture was concentrated and purified by flash chromatography (75 :25 hexane:ether). The resulting alcohol was subjected to similiar bromination conditions. The alcohol (3.73 mmol, 0.65 g) was dissolved in distilled methylene chloride (6.0 mL) and cooled to 0°C. The reaction flask was purged with argon for 10 minutes. Triphenylphosphine (4.48 mmol, 1.17 g) was added and allowed to dissolve into solution. Carbon tetrabromide (4.11 mmol, 1.36 g) was slowly added in parts. The reaction was monitored by TLC. Workup entailed an extraction with brine and methylene chloride. The organic layer was dried

with anhydrous magnesium sulfate and concentrated. The product was isolated by flash chromatography on silica gel (hexane/ether 65:35), leaving a residual oil **4-17** (0.55 g, 62%).

4-17 : R_f= 0.88 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 6.96 (m, 1H), 6.12 (m, 1H), 4.2 (m, 4H), 3.81 (t, 6.0 Hz, 2H), 3.49 (t, 6.0 Hz, 2H), 1.29 (t, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) 165.97, 143.47, 121.57, 70.54, 69.46, 60.29, 30.00, 14.09; IR (neat): 2980.5, 2359.8, 1717.2, 1662.2, 1445.9, 1368.0, 1302.8, 1277.9, 1176.6, 1121.2, 1040.4, 970.2 cm^{-1}; HRMS calcd for $C_8H_{13}O_3Br$ 236.0248, found 236.0126.

General procedure for radical cyclizations. Bromide **4-14** (0.0035 mmol, 0.015 g) and methylene chloride (0.5 M) were added to an argon flushed, oven-dried, round bottom flask. The Lewis acid (2 equiv.) was also added to the reaction vessel and allowed to stir under argon at room temparture for 15 minutes. The reaction mixture was then cooled to -78 °C with a dry ice/acetone bath. Tributyltin hydride (0.035 mmol, 0.035 mL) and triethylborane (1M in hexane) (0.017 mmol, 0.047 mL) were then added to the solution in that order. After all the reagents were allowed to stir at -78 °C for ten minutes, oxygen was bubbled into the mixture for five minute intervals every three hours. The reaction was monitored by TLC until completion. The mixture containing **4-15** was concentrated and subjected directly to saponification conditions without further purification to give **4-16** (0.010 g, 82%).

(2-(S)-Tetrahydrofuranyl)acetic acid 4-16.[65] The cyclized adduct **4-15** (0.95 mmol, 0.15 g) was dissolved in a 5:1 THF:H_2O solution and stirred at room temperature. To this flask, 10 equiv. of LiOH was added. The resulting reaction mixture was heated at reflux for three hours. Reaction progress was monitored by TLC. The reaction mixture was first washed with ether to remove any organic contaminants, followed by neutralization of the basic solution with 2M HCl. An ethyl acetate wash removed the reprotonated alcohol product. Further acidification to pH 2 provided acid **4-16** (0.09 g, 72 %).

4-16 : R_f = 0.73 (35:65 EtOAc:Hex); ^{1}H NMR ($CDCl_3$) 3.98 (dd, 7,8 Hz, 1H), 3.88 (m, 1H), 3.8 (m, 2H), 3.45 (dd, 7,8 Hz, 1H), 2.62 (m, 1H), 2.45 (d, 8 Hz, 2H), 2.15 (m, 1H), 1.6 (m, 1H).). All spectral data is in agreement with known literature values.[65]

(-)-Diethyl 2,3-O-isopropylidene-L-tartrate 5-13. To a solution of diethyl-L-tartrate **5-12** (76 mmol, 15.7 g) and dimethoxypropane (50 mmol, 61 mL) in acetone (182 mL) was added *p*-toluenesulfonic acid (2 mmol, 0.38 g). The vessel was purged of all oxygen by degassing with argon for 20 min. The solution was stirred at room temperature overnight. The resulting solution was neutralized with sodium bicarbonate and extracted with diethyl ether. The concentrate resulted in a yellow oil which was subjected to flash chromatography to give **5-13** (16.0 g , 85%).

5-13 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 4.73 (s, 2H), 4.24 (q, 4H), 1.47 (s, 6H), 1.25 (t, 6H). The isolated product is identical in all respects to a commercial sample obtained from Aldrich Chemical Co.

(+)-2,3-O-Isopropylidene-L-threitol 5-14. Lithium aluminum hydride (36 mmol, 1.37 g) was stirred under argon in THF (48 mL) for 5 minutes. Slowly, (-)-dimethyl 2,3-O-isopropylidene-L-tartrate **5-13** (24 mmol, 6.0 g) was added dropwise until all of the compound was transferred. The reaction was stirred continuously overnight to ensure completion. Workup procedures involved quenching the excess hydride with a Celite/$NaSO_4 \cdot H_2O$. The reaction mixture was then diluted to twice its volume with ethyl acetate. The lithium/aluminum salts were filtered through a porous frit and the resulting filtrate was concentrated down and chromatographed on silica to give **5-14** (2.6 g, 67%).

5-14 : ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.9 (s, 2H), 3.7 (s, 4H), 3.5 (s, 1H), 1.38 (s, 6H). The isolated product is identical in all respects to a commercial sample obtained from Aldrich Chemical Co.

Monobenzylated 2,3-O-isopropylidene-L-threitol 5-15. Under an argon environment, sodium hydride (60% in oil, 0.53 g, 13.2 mmol) was washed with pentane three times to ensure removal of the protective mineral oil. After the residual pentane was removed by vacuum, a solution containing the (+)-2,3-O-isopropylidene-L-threitol **5-14** (12 mmol, 1.95 g) and THF (16 mL) was added dropwise to the reaction vessel. The mixture was allowed to stir for one h. Benzyl bromide (24 mmol, 4.1 g) was then added slowly. The reaction progress was followed by TLC. Upon consumption of the starting material, approximately 4 h, the reaction mixture was poured into a separatory funnel and the organic residue was extracted with ether.

The ethereal solution was concentrated and the resulting oil chromatographed to give **5-15** (1.65 g, 55%).

5-15 : R_f= 0.29 (35:65 EtOAc:Hex) ; [α] = - 4.1° (c = 0.04, ethanol) ; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.35 (s, 4H), 4.55 (s, 2H), 4.0 (m, 2H), 3.65 (m, 4H), 2.6 (s, 1H), 1.4 (s, 6H); ^{13}C NMR ($CDCl_3$) δ137.4, 128.3, 127.6, 109.2, 79.4, 76.4, 73.5, 70.2, 62.2, 26.8, 26.7; exact mass (CI) for $C_{14}H_{20}O_4$ calcd. for 253.1439, found 253.1439.

Soluble chloromethylated polystyrene 5-10. To a solution of styrene (144 mmol, 15 g) and 4-(chloromethyl)styrene (22.3 mmol, 3.4 g,) in benzene (60 mL) was added 2,2-azobiisobutylnitrile (AIBN) (0.74mmol, 0.12 g). The vessel was purged of all oxygen by degassing with argon for 20 min. The solution was stirred at 70°C for 40 h. The mixture was then poured into –78°C methanol to obtain the crystalline chloromethylated polystyrene product and repeatedly washed to remove the excess reagents. The solid was dried overnight by vaccum to give **5-10** (6.0 g).

5-10 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.3-6.2 (m, 30H, Ar-H), 4.55 (s, 2H, CH_2-Ar), 2.2-0.9 (m, 19H, -CH_2-CH_2-). The chlorine content of the polymer was determined by ^{1}H NMR; a value of 1.5 mmol per 1g of polymer was determined. See spectra in the Appendix.

Acetonide mounted polymer 5-16. In an argon flushed, round bottom flask, sodium hydride (60%) (0.24 g, 6 mmol) was washed with pentane three times to ensure removal of the protective mineral oil. After the residual pentane was removed by vacuum, a solution containing the monobenzylated-protected diol **5-15** (5.6 mmol,

1.4 g) and dimethyl acetamide (DMA) (10 mL) was added dropwise to the reaction vessel. The reaction was allowed to stir for one hour. The polystyrene polymer **5-10** (2.0 g) was dissolved in 50 ml of DMA. After the one hour reaction time, the dissolved polymer solution was added to the reaction flask. The resulting solution was stirred overnight. The reaction mixture was then poured into –78°C methanol while swirling the receiver flask. White crystals were collected shortly after by passing the solution through a course frit. The crystals were kept under a high vacuum pressure for one h. to facilitate drying. The loading yield of the mono-benzylated acetonide **5-16** onto the polymer was determined by NMR; the reaction yield was 96%.

5-16 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.3-6.2 (m, 43H, Ar-H), 4.45 (m, 4H), 4.05 (s, 2H), 3.55 (s, 4H), 2.0-0.9 (m, 36H). [α] – 2.4° (c = .0067, tertrahydrofuran); See spectra in the Appendix.

Preparation of 5-17. The mounted diol **5-16** (2.0g) was dissolved in 25 mL of freshly distilled THF in a clean round bottom flask. While the solution was being stirred, 1.5 mL of concentrated hydrochloric acid was added dropwise to the reaction flask. The reaction was allowed to stir overnight. The resulting solution was poured into a separatory funnel and quenched with sodium carbonate. The organic layer was extracted with ethyl acetate, dried with sodium sulfate, filtered and concentrated. The resulting oil was dissolved in a small amount of THF and poured into cold (-78°C) methanol. (Note: when working with higher content polymers, a cold solution of hexane may be necessary to crash out the NCPS). The resulting crystals were filtered

and dried on a high vacuum pump. The mass yield was 2.0 g of material at 90% conversion to the free diol according to NMR.

5-17 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.4-6.2 (m, 43H, Ar-H), 4.5 (m, 4H), 3.7 (m, 6H), 3.0 (m, 2H), 2.0-0.9 (m, 33H). See spectra in the Appendix.

Ketalization of 4-*tert*-butyl cyclohexanone 5-18. Compound **5-17** (0.8 mmol, 1.0 g) was dissolved in freshly distilled benzene (50 ml). Also added to the flask was 4-*tert*-butyl cyclohexanone **5-19** (2.4 mmol, 0.37 g) and a catalytic amount of *p*-toluenesulfonic acid. The round bottom containing the above mixture was connected to a Dean-Starke trap and condenser. The reaction was allowed to stir overnight at a gentle reflux of 80°C. Workup of the resulting solution entailed concentrating the mixture and dissolving the crashed out polymer in a minimum amount of THF. This mixture was slowly added to a cold (-78°C), stirred methanol solution. Upon addition of the polymer to the receiver flask white crystals were observed. The crystal/methanol solution was filtered through a porous frit and the collected crystals of **5-18** were allowed to dry on high vacuum for 2 hours (0.95 g).

5-18 : ^{1}H NMR (300 MHz,$CDCl_3$) 7.4-6.2 (m, 25H, Ar-H), 4.5 (m, 4H), 4.05 (m, 2H), 3.58 (s, 4H), 2.0-0.9 (m, 27H), 0.85 (s, 9H). The ketalization yield of 4-*tert*-butyl cyclohexanone was determined by NMR; the reaction yield was 98%. See spectra in the Appendix.

Deprotection of 4-*t*-butyl cyclohexanone. The ketal-mounted polymer **5-18** was dissolved in 25 mL of freshly distilled THF. Concentrated sulfuric acid (2 mL) was

added slowly. The resulting solution was stirred overnight. Workup procedures involved pouring the mixture into a separatory funnel and quenching the acid with sodium carbonate. The organic layer was extracted with ethyl acetate, dried with sodium sulfate, filtered and concentrated. The resulting oil was dissolved in a small amount of THF and poured into cold (-78°C) methanol while swirling the receiver flask. White crystals were collected shortly after by passing the solution through a course frit. The crystals were kept under high vacuum pressure for one hour to facilitate drying. The original carbonyl was recovered (0.065g, 85%).

5-19 : R_f= 0.58 (35:65 EtOAc:Hex) ; ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 4H), 2.1 (m, 2H), 1.45 (m, 3H), 0.93 (s, 9H). The isolated product **5-19** is identical in all respects to a commercial sample obtained from Aldrich Chemical Co.

The free diol **5-17** was also recovered in a 75 percent yield. The polymer was reused in subsequent reactions. ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.4-6.2 (m, 43H), 4.5 (m, 4H), 3.7 (m, 6H), 3.0 (m, 2H), 2.05-0.9 (m, 33H).

Ketalization of 1,2-cyclohexanedione 5-24. Diol **5-17** (1.9 mmol, 1.75 g) was dissolved in freshly distilled benzene (50 ml). Also added to the flask was 3 eqv. of 1,2-cyclohexanedione (0.64 g, 5.7 mmol) and a catalytic amount of *p*-toluenesulfonic acid. To drive the reaction forward, 0.5 g of anhydrous sodium sulfate was added to the reaction mixture. The round bottom containing the above mixture was connected to a Dean-Starke trap and condenser. The reaction mixture was allowed to stir overnight at a gentle reflux (80°C). Workup of the resulting solution entailed concentrating the mixture and re-dissolving the precipitated polymer in a minimum

amount of THF. This mixture was slowly added to a cold (-78°C), stirred methanol solution. Upon addition of the polymer to the methanol flask, tan crystals were observed. The crystal/methanol solution was filtered through a porous frit and the collected crystals were allowed to dry on high vacuum for 2 h. The ketalization yield of 1,2-cyclohexanedione was determined by NMR; the reaction yield was 85 %.
5-24 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.3-6.2 (m, 39H), 4.5 (m, 4H), 4.1 (m, 2H), 3.7 (m, 4H), 2.4 (m, 2H), 2.1-0.85 (m, 35H). See spectra in the Appendix.

Grignard reaction with the 1,2 cyclohexanedione ketal 5-25. The ketal-mounted polymer **5-24** (1.7 mmol, 1.75 g) was dissolved in 25 mL of freshly distilled THF and degassed with argon for 20 min. The reaction flask was submerged in a dry ice/acetone bath and allowed to cool for 10 min. While stirring, methylmagnesium bromide (1.14 g, 9.5 mmol) was added dropwise until all of the reagent had been transferred. The resulting mixture was gradually warmed to room temperature and allowed to stir overnight. Workup procedures involved extracting the polymer with ethyl acetate and removing the magnesium salts by washing with ammonium chloride three times. The organic layer was dried with sodium sulfate, filtered and concentrated. The resulting oil was dissolved in a small amount of THF and poured into cold (-78°C) methanol while swirling the receiver flask. White crystals of **5-24** were collected shortly after by passing the solution through a course frit. The crystals were kept under a high vacuum pressure for one hour to facilitate drying.
5-25 : ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.3-6.2 (m, 39H), 4.45 (m, 4H), 4.1 (m, 2H), 3.5 (m, 4H), 2.0-0.85 (m, 39H). See spectra in the Appendix.

Deprotection of the Grignard adduct 5-26. The ketal-mounted polymer **5-25** was dissolved in 25 mL of freshly distilled THF. Concentrated sulfuric acid (2 mL) was added slowly. The resulting solution was stirred for 24 hours. Workup procedures involved pouring the mixture into a separatory funnel and quenching the acid with sodium carbonate. The organic layer was extracted with ethyl acetate, dried with sodium sulfate, filtered and concentrated. The resulting oil was dissolved in a small amount of THF and poured into cold (-78°C) methanol while swirling the receiver flask. White crystals were collected shortly after by passing the solution through a course frit. The crystals were kept under a high vacuum pressure for one hour to facilitate drying. According to NMR, very little, if any, of the ketal was deprotected. The methanol filtrate was concentrated, but the remaining residue did not contain the desired α-hydroxy ketone.

APPENDIX
HPLC CHROMATOGRAMS AND SPECTRAL DATA

The ^{1}H NMR spectra of selected compounds from Chapter 3 and 5 are illustrated in this appendix. The spectra along with the proposed structure are shown. The chiral HPLC work from Chapter 3 and 4 is also presented.

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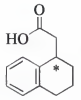

racemate
TBTH, 80°C, AIBN

Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	1.613	Err1	1244698	8415678	49.893
2	3.423	N1	2629	18977	0.112
3	3.625	N2	566182	8102370	48.035
4	4.465	N3	11607	232156	1.376
5	4.740	N4	7047	97835	0.580
	6.866	N	157	274	0.001
Total Area				16887290	99.997

UV detector, 254 nm

(S)-*tert*-leucine (R)-1-(α-naphthyl)

ethylamine column, 250 x 4.6mm ID

70:30 CH_3OH:H_2O mobile phase

1 mL/min flow rate

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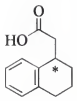
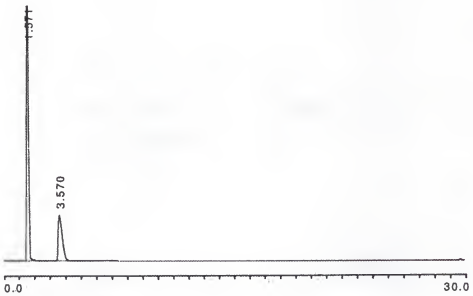


no L.A., 0°C, Et_3B/O_2



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	1.571	Err1	1267412	7430959	68.198
	3.451	N1	1221	5913	0.054
2	3.570	N2	223536	3244193	29.773
3	5.131	N3	3681	172063	1.579
4	5.756	N4	2162	43014	0.394
Total Area				10896142	99.998

UV detector, 254 nm

(S)-*tert*-leucine (R)-1-(α-naphthyl)

ethylamine column, 250 x 4.6mm ID

70:30 CH_3OH:H_2O mobile phase

1 mL/min flow rate

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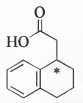
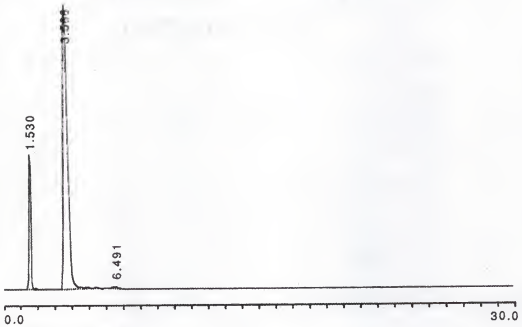


$Yb(OTf)_3$, -78°C, Et_3B/O_2



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	1.530	N1	532781	2267365	12.039
2	1.851	N2	5110	52294	0.277
3	2.226	N3	1567	19598	0.104
4	3.566	Err	1132470	16028294	85.109
5	4.861	N2	7591	180657	0.959
6	5.410	N3	6034	106491	0.565
7	6.491	N	6906	177900	0.944
Total Area				18832599	99.997

UV detector, 254 nm

(S)-*tert*-leucine (R)-1-(α-naphthyl)

ethylamine column, 250 x 4.6mm ID

70:30 $CH_3OH:H_2O$ mobile phase

1 mL/min flow rate

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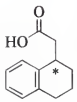

$MgBr_2OEt$, -78°C, Et_3B/O_2

Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	1.521	N1	492915	2093210	6.756
2	1.783	N2	5015	30347	0.097
3	1.946	N3	3240	36306	0.117
4	2.253	N4	14702	168614	0.544
5	2.688	N5	3562	67401	0.217
6	3.401	N1	5169	14695	0.047
7	3.545	Err	1277532	28490876	91.960
8	5.413	N3	4221	80059	0.258
Total Area				30981508	99.996

UV detector, 254 nm

(S)-*tert*-leucine (R)-1-(α-naphthyl)

ethylamine column, 250 x 4.6mm ID

70:30 CH_3OH:H_2O mobile phase

1 mL/min flow rate

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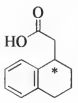
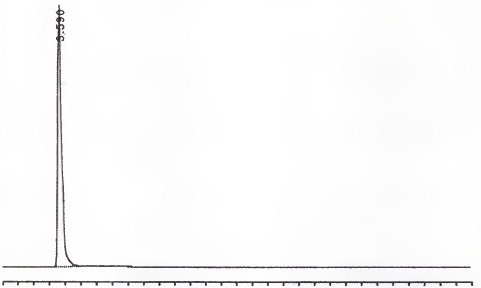


$ZnCl_2$, -78°C, Et_3B/O_2



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
	3.451	N1	2349	5112	0.029
1	3.590	Err	1278105	17297932	99.970
Total Area				17303044	99.999

UV detector, 254 nm

(S)-*tert*-leucine (R)-1-(α-naphthyl)

ethylamine column, 250 x 4.6mm ID

70:30 CH_3OH:H_2O mobile phase

1 mL/min flow rate

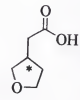
Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	3.575	6411313	51.780	372100	60.595	MM
2	4.733	5970433	48.220	241981	39.405	MM
Totals		12381746	100.000	614081	100.000	

RI detector, T = 25°C

(S)-*tert*-leucine (R)-1-(α-naphthyl) ethylamine column, 250 x 4.6mm ID

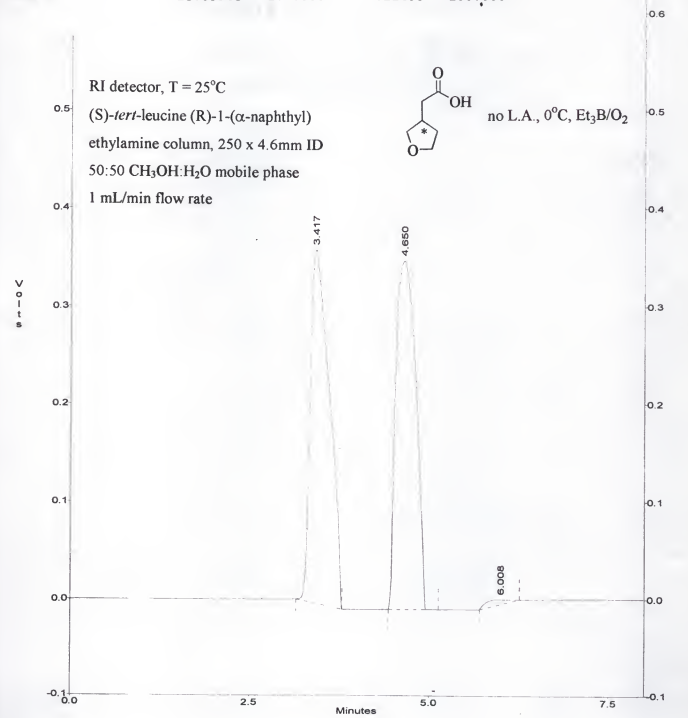
50:50 CH_3OH:H_2O mobile phase

1 mL/min flow rate



racemate
TBTH, 80°C, AIBN

Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	3.417	6648703	48.319	360591	49.984	BB
2	4.650	6981167	50.735	356014	49.350	BB
3	6.008	130093	0.945	4803	0.666	BV
Totals		13759963	100.000	721408	100.000	



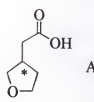
Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	2.092	1775	0.042	103	0.055	BB
2	3.633	3168530	75.637	147034	78.137	BV
3	4.783	1018795	24.320	41037	21.808	VV
Totals		4189100	100.000	188174	100.000	

RI detector, T = 25°C

(S)-*tert*-leucine (R)-1-(α-naphthyl) ethylamine column, 250 x 4.6mm ID

50:50 CH_3OH:H_2O mobile phase

1 mL/min flow rate



$AlEt_2Cl$, -78°C, Et_3B/O_2

Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	3.608	4690123	77.890	230959	81.747	BV
2	4.775	1331367	22.110	51569	18.253	VV
Totals		6021490	100.000	282528	100.000	

RI detector, T = 25°C

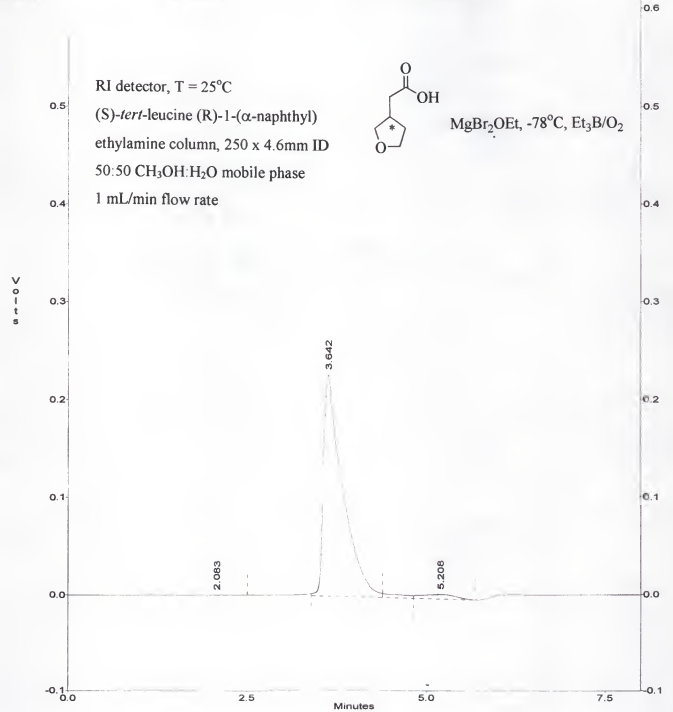
(S)-*tert*-leucine (R)-1-(α-naphthyl) ethylamine column, 250 x 4.6mm ID

50:50 CH_3OH:H_2O mobile phase

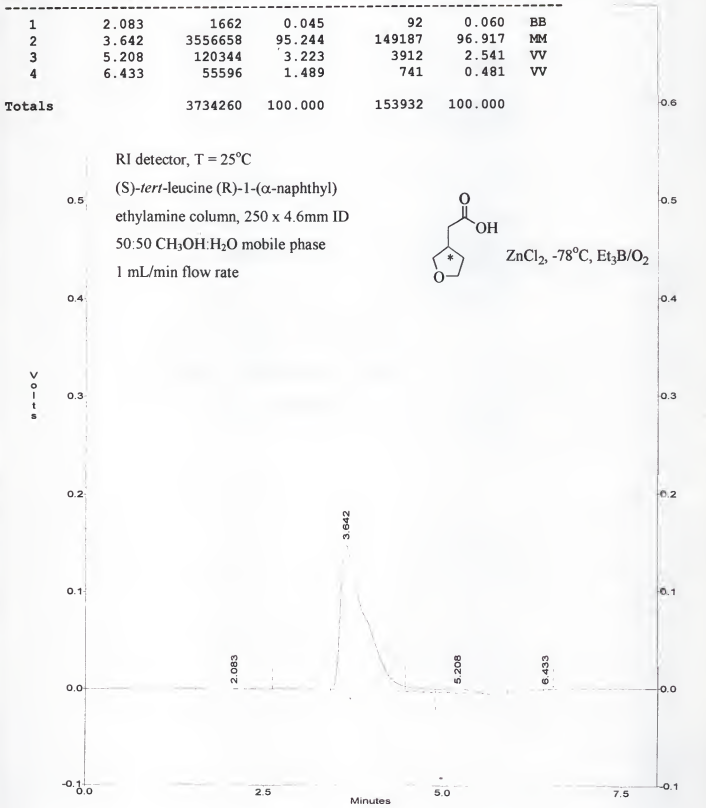
1 mL/min flow rate

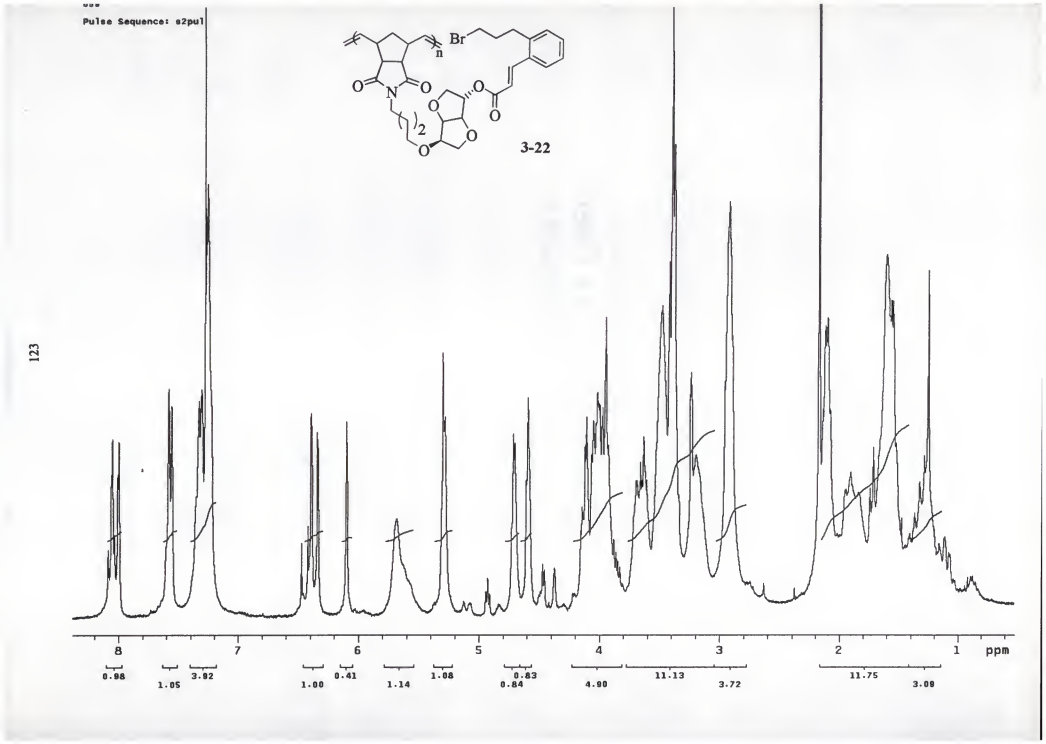
$Yb(OTf)_3$, -78°C, Et_3B/O_2

Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	2.083	2775	0.064	180	0.078	BV
2	3.642	4185671	96.386	226507	97.979	MM
3	5.208	154158	3.550	4491	1.943	VV
Totals		4342604	100.000	231178	100.000	



Pkno	Mig. Time	Area	Area%	Height	Height%	Flags
1	2.083	1662	0.045	92	0.060	BB
2	3.642	3556658	95.244	149187	96.917	MM
3	5.208	120344	3.223	3912	2.541	VV
4	6.433	55596	1.489	741	0.481	VV
Totals		3734260	100.000	153932	100.000	

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O
O
O
2
3-22
8
7
6
5
4
3
2
1
ppm
0.98
1.05
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1.00
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1.14
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0.84
4.80
11.13
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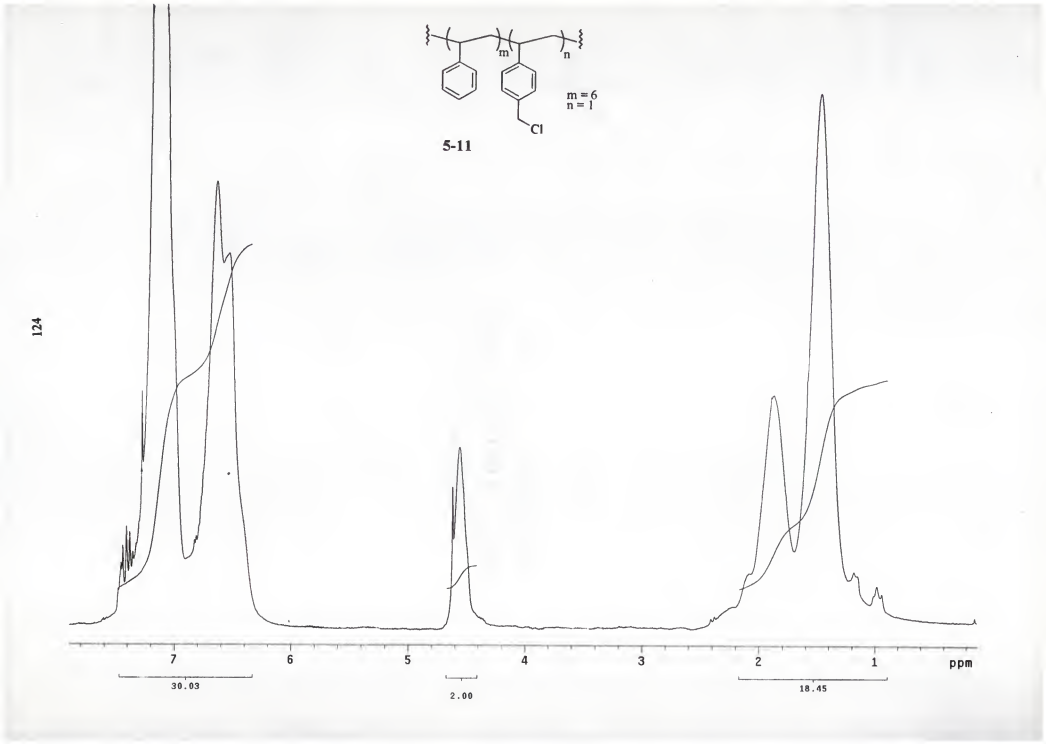
11.75
3.08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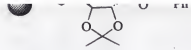
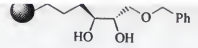
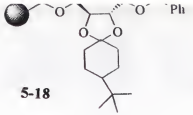


5-16



5-17



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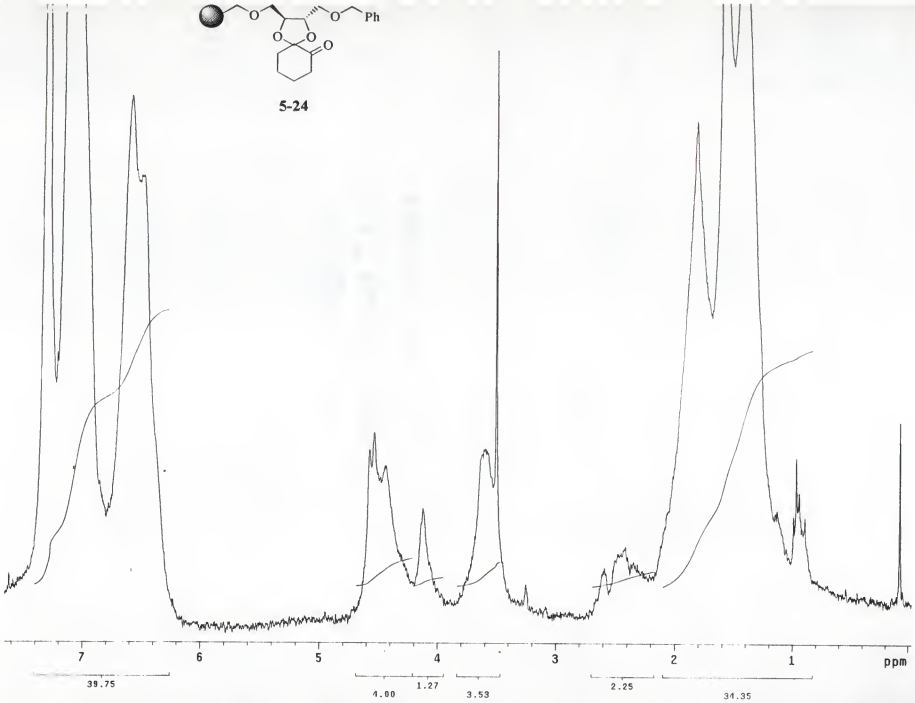
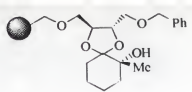


5-24



5-25

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BIOGRAPHICAL SKETCH

Jennifer Spring Lombardi was born in Attleboro, Massachusetts on April 22, 1974. She grew up in southeast New England in locations varying from Harrisville, RI to Dighton, MA. She attended Dighton-Rehoboth High School where she was first challenged by chemistry. In fact, Mr. Harwood's AP chemistry course was the first class to give her serious trouble. Insistent on mastering this subject, Jennifer majored in chemistry her first semester at Suffolk University in Boston, Ma. Dr. Maria Miliora instilled in her the challenge of organic chemistry. Dr. Miliora acted as a role model for the remaining years of Jennifer's chemistry education. Because teaching has always been her goal and passion, Jennifer decided to continue her education to the Ph.D. level. Under the advisement of Dr. Eric Enholm, Jennifer has matured significantly in the science, especially in the research facet. It was during these four and a half years of graduate study that Jennifer met her husband Andrew and took his name, Cottone, in October of 1999. Throughout many years of higher education, Jennifer's parents, Paul and Marilyn, and family have been undaunting in their love and support. Presently, Jennifer Cottone is a chemistry teacher at St. Andrew's School in Middletown, Delaware.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

J. Eric Enholm, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

David H. Powell
Scientist of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

Tomas Hudlicky
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

James A. Deyrup
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree Doctor of Philosophy.

Kenneth Sloan
Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 2000

Winfred M. Phillips
Dean, Graduate School